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HTA REPORT

HIFU for the treatment of prostate cancer

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HTA REPORT

High Intensity Focused Ultrasound (HIFU) for the treatment of prostate cancer

INDEX

Foreword

This year Agenas has produced a HTA report on the treatment of prostate cancer by HIFU ablation on the behalf of the of the Italian Ministry of Health. Such report comes from a long and laborious process of consultation with experts, reviewers (internal and external), manufacturers, and other stakeholders.

The HTA report is developed from the following question: "Based on the available evidence, is it possible to provide guidance on the use of HIFU for the treatment of localised prostate cancer within the National Health Service (NHS)?". Hence, other than exploring effectiveness and safety, data on the diffusion and costs of the technology have been collected and analysed.

The latest evidence on clinical effectiveness have been synthesised by a systematic review of literature while, to obtain a comprehensive overview on the diffusion of the HIFU technology as well as on some utilisation trends, a survey across all the NHS centres has been carried out.

At the time of writing the HIFU procedure is not linked to a specific reimbursement fee. Nevertheless the diffusion of the technology across the country is relevant: 29 NHS centres are able to provide the treatment.

From our findings we can state that the HIFU procedure for localised prostate cancer is only supported by evidence from non-comparative studies and this suggests its use as an "investigational" technique that at least should be supported by evidence-generation tools (e.g. registers).

The lack of comparative effectiveness data hampered our economic analysis, in particular limiting it to a cost analysis. Such data should be available after the ongoing trials (e.g. PIVOT, ProtecT study, START trial) will be concluded allowing more in-depth analyses.

Fulvio Moirano

Executive Director of Agenas

Executive summary

One-liner

We assessed effectiveness and safety of the High Intensity Focused Ultrasound (HIFU) ablation of prostate cancer and reported on the diffusion and costs of the technology in Italy.

Background

Prostate cancer represents one of the most common cancers in men. Its incidence increases with age and is rare before 50 years of age. Localised prostate cancer includes a tumour confined to the prostatic capsule or at most with an extra-prostatic extension (T1 and T2 patients), without spread to seminal vescicles or regional lymph nodes, and/or other organs. The onset of prostate cancer is asymptomatic in most cases. However, increased urinary frequency, weak urinary stream, urinary obstruction, lower urinary tract infections and inadequate bladder emptying may be found. Other symptoms may include erectile dysfunction and haematuria. The diagnosis of prostate cancer is established by transrectal ultrasound guided biopsy, typically after abnormal PSA blood level, digital rectal examination, or both.

In Europe the incidence rate of prostate cancer is 55 cases per 100,000 inhabitants and the mortality rate of 22.6 deaths per 100,000 people. In Italy prostate cancer is the most common cancer in men with an estimated 36,500 new cases in 2008.

According to the latest guidelines, T1-T2 patients have conservative as well as curative options for cancer management. There is no definitive evidence for the superiority of any one treatment over the others and the merits and risks of each are still debated. The best treatment is related to the patient's age, his health status, his acceptance of the treatment-related complications, and contraindications for surgery.

HIFU ablation represents a new minimally invasive treatment for prostate cancer that destroys tissues by thermal and mechanical effects without damage adjacent tissues.

Objective

To assess whether, based on available evidence, is it possible to provide guidance on the use of HIFU for the treatment of localised prostate cancer within the Italian NHS.

Methods

We carried out searches of the available evidence from both primary and secondary literature, to identify and assess the effectiveness and safety of HIFU treatment for prostate cancer compared to alternative treatments in the target population, i.e. males with localised prostate cancer (T1-T2), with low or intermediate risk disease who are being treated with curative intent. We carried out a national survey across all the centres performing the HIFU procedure aimed to get all the relevant information on the use of the technology. We carried out a literature review of economic studies published between 2008 and 2010. We carried out a cost analysis, processing all the costs related to the HIFU treatment.

Results

We updated the latest systematic review with the most recent evidence (Warmuth et al.). We included 17 studies from the review by Warmuth et al. and further 6 studies.

The 23 studies we extracted were all observational case series. Population within the studies ranged from 19 to 517 patients. All the included studies presented limited mean follow-up periods. The Ablatherm HIFU system was used in 13 studies (1,920 patients) and the Sonablate 500 HIFU system was used in 10 studies (1,311 patients). Ten of the 23 studies reported whether TURP was performed before or concomitant to HIFU procedure. Eighteen of the 23 studies reported whether neoadjuvant androgen-deprivation therapy was administrated to patients.

Biochemical disease-free survival rate was reported in all the studies but one as well as negative biopsy rate (not reported in 4 studies). Overall survival rate, as well as prostate cancer-specific survival rate, was generally not reported (only in 5 and 7 studies respectively). Quality of life and patient-related outcomes as well as functional assessment of urinary flow, were assessed in 7 studies. All the studies reported in detail the adverse events related to urinary tract and rectum while pain was not often reported. The analysis of the sexual potency was performed pre- and post-operatively in many of the studies.

The safety profile of the HIFU treatment can be summarised taking account of: occurrence of rectourethral fistula, adverse events related to the urinary tract, and urinary incontinence.

Questionnaires have been sent to 29 centres; we received 14 questionnaires back.

We carried the survey across 29 centres. Nine centres purchased the HIFU system and 17 rented it; 3 centres did not provide this kind of information.

We estimated the cost per HIFU procedure by summing all the cost elements calculated within the following assumptions: cost of the technology (rental), cost of the human resources involved (1 or 2 physicians, and 1 or 2 nurses) and cost of drugs/materials/disposables used. We estimated a minimum total cost of € 2,938.60 and a maximum total cost of € 4,610.57 for the Ablatherm HIFU system. It was not possible to estimate the total cost for the Sonablate 500 HIFU system because the main cost elements were not available.

Due to lack of results from the literature search for economic studies it was not possible any data matching. Using the TUC 2009 (*Tariffa Unica Convenzionale*, Reimbursement fee from the Italian Ministry of Health) we linked the HIFU procedure to the DRGs 306 and 307, respectively "Prostatectomy with complications" (€ 4,630.93) and "Prostatectomy without complications" (€ 2,868.85). As our survey showed that in most cases the HIFU treatment is performed after the TURP procedure, we included the cost of TURP in the costs calculation. The procedure is linked to DRGs 336 and 337, "Transuretral Prostatectomy with complications" (€ 3,574.32) and "Transuretral Prostatectomy without complications" (€ 2,717.82). Finally, linking the HIFU procedure with the TURP procedure, assuming the procedures are provided in two different admissions, its cost ranged from € 5,609.62 to € 8,242.30. We have not taken into account the costs associated with post-interventional pathway and complications of treatment that may require costly interventions in addition to impact on patient quality of life.

Conclusions

Evidence from our systematic review did not allow us to make a final statement about the comparative effectiveness of HIFU ablation versus the other options. No RCTs or other comparative studies had been published. Only non-comparative retrospective studies have been published reporting on large groups of patients for long follow-up periods. We believe that the lack of trials is the main problem in the field of medical devices and surgical interventions assessment.

Although a specific reimbursement fee for the HIFU procedure does not exist, the technology is widely used in Italy. We suggest considering HIFU as an investigational treatment since the mechanisms of action and short-term effectiveness are already known but long-term comparative data are expected.

Synthesis

Clinical problem and target population

Prostate cancer represents one of the most common cancers in men. Its incidence increases with age and is rare before 50 years of age.

Prostate cancer can be classified as localised, locally advanced, advanced (or metastatic), and hormone refractory. Localised prostate cancer includes a tumour confined to the prostatic capsule or at most with an extra-prostatic extension (T1 and T2 patients), without spread to seminal vescicles or regional lymph nodes, and/or other organs. The onset of prostate cancer is asymptomatic in most cases. However, increased urinary frequency, weak urinary stream, urinary obstruction, lower urinary tract infections and inadequate bladder emptying may be found. Other symptoms may include erectile dysfunction and haematuria.

The diagnosis of prostate cancer is established by transrectal ultrasound guided biopsy of the prostate which is typically prompted by an abnormality in the PSA blood test, digital rectal examination, or both. In Europe the incidence rate of prostate cancer is 55 cases per 100,000 inhabitants and the mortality rate of 22.6 deaths per 100,000 people. In Italy prostate cancer is the most common cancer in men with an estimated 36,500 new cases in 2008.

When considering treatment options, the patient, their family and physician must take into account his life expectancy, his acceptance of the treatment-related complications, contraindications for surgery, and tumour differentiation grade. According to the latest EAU Guidelines, patients with T1-T2 staging have conservative as well as curative options for cancer management.

Description of the technology

High Intensity Focused Ultrasound (HIFU) ablation represents a new treatment for prostate cancer management. HIFU destroys tissues by a thermal and mechanical effect.

The main elements of an HIFU system are: the endorectal probe that encloses a piezoelectric or piezoceramic transducer to generate ultrasound waves which are focused into a focal point by a concave or parabolic configuration and an ultrasound scanner for treatment planning; the visualisation system, i.e. the monitor that allows to set and control the treatment procedure through echographic screening.

Two HIFU systems for prostate cancer management are commercially available in Italy: the Ablatherm® HIFU (manufactured by EDAP-Technomed®) and the Sonablate 500® (manufactured by Focus Surgery®).

HIFU treatment is generally administered transrectally using local, regional or general anaesthesia.

The procedure can be repeated over time and can be performed in day-surgery, outpatient or inpatient settings. HIFU may be preceded by a TURP (transurethral resection of the prostate). HIFU ablation is proposed as alternative to the following standard treatments of localised prostate cancer in primary

therapy: i) Active Surveillance; ii) Watchful Waiting; iii) Radical Prostatectomy; iv) Radiotherapy; v) Hormone Therapy.

There is no definitive evidence for the superiority of any one treatment over the others and the merits and risks of each are still debated. The best treatment is related to the patient's age, his health status, the cancer stage and the personal preference.

Objectives of the assessment

Objectives of this HTA report were the following: i) To assess and analyse effectiveness and safety data from the scientific literature on the HIFU treatment of localised prostate cancer compared to standard treatments; ii) To describe the level of adoption and utilisation of the technology within the providers of the Italian NHS and to investigate the availability of (non-frequent) alternative treatment options; iii) To perform an economic analysis on the utilisation of the technology within the Italian clinical practice; iv) To assess patient acceptability of the HIFU treatment.

Methods

We carried out searches of the available evidence from both primary and secondary literature, to identify and assess the effectiveness and safety of HIFU treatment for prostate cancer compared to alternative treatments in the target population, i.e. males with localised prostate cancer (T1-T2), with low or intermediate risk disease who are being treated with curative intent.

Searches for secondary literature were run on the Cochrane Database of Systematic Review and on the CRD database. In particular, we accessed the DARE (Database of Abstracts of Reviews of Effects) and the HTA Database to identify systematic reviews and HTA reports respectively. We considered any document published in English or Italian from 1st January 2000 to 6th October 2010.

Systematic searches for primary literature were run on three main databases: EMBASE, Cochrane Library and Medline. We considered comparative as well as observational case series whether comparative studies were not available. We included studies assessing the HIFU treatment and published in English or Italian from 1st January 2000 to 17th December 2010. We considered also information from "gray literature".

We carried out a national survey across all the centres performing the HIFU procedure aimed to get all the relevant information on the use of the technology; we built a structured questionnaire to collect data on the number of procedures performed in the centres, on the clinical pathways followed, on the acquisition of the technology, and on the costs. Data for 2008 and 2009 were collected.

We carried out a literature review of economic studies published between 2008 and 2010 identified in the main databases: CRD, HEED, PubMed, EMBASE and Cochrane Library.

We carried out a cost analysis, processing all the costs related to the HIFU treatment as well as those related to the other treatment options.

Results

According to our research protocol, we decided to update the latest systematic review with the most recent evidence. Such review was by Warmuth et al. and we decided to use it as our evidence base and

update the searches to 17th December 2010. We included: i) studies included in the review by Warmuth et al. that met our inclusion criteria; ii) studies meeting our inclusion criteria published from 1st January 2000 to 17th December 2010.

We included 17 studies from the review by Warmuth et al. We did not find any study to update evidence. However we were able to include 6 studies that were previously excluded by Warmuth et al. as they reported on populations of less than 50 patients. We carried out the data extraction from the 23 studies.

The 23 studies we included were all observational case series. No RCTs or comparative studies were found. Population within the studies ranged from 19 to 517 patients. Mean age was more than 70 years in most of the studies. All the included studies presented limited mean follow-up periods (the longer was 77 ± 12 months). The Ablatherm HIFU system was used in 13 studies (1,920 patients) and the Sonablate 500 HIFU system was used in 10 studies (1,311 patients). In some cases prototypes or old versions of both the HIFU systems have been used and this limits the generalisability of results.

Ten of the 23 studies reported whether TURP was performed before or concomitant to HIFU procedure; no information about TURP were reported in 10 studies. Eighteen of the 23 studies reported whether neoadjuvant androgen-deprivation therapy (ADT) was administrated to patients; No information about neoadjuvant ADT was reported in 5 studies. Biochemical disease-free survival rate (as mean PSA nadir or PSA level at final follow-up visit) was reported in all the studies but one as well as negative biopsy rate (not reported in 4 studies). Overall survival rate, as well as prostate cancer-specific survival rate, was generally not reported (only in 5 and 7 studies respectively). Quality of life and patient-related outcomes as well as functional assessment of urinary flow, were assessed in 7 studies. All the studies reported in detail the adverse events related to urinary tract and rectum while pain was not often reported. The analysis of the sexual potency was performed pre- and post-operatively in many of the studies.

The safety profile of the HIFU treatment can be summarised taking account of: occurrence of rectourethral fistula (from 0.9% to 1.2% in the larger groups); occurrence of adverse events related to the urinary tract (urethral stenosis or obstruction, and infections: up to 60% and 58% of the patients treated respectively); urinary incontinence (different grades reported in up to 24% of the patients treated).

Questionnaires have been sent to 29 centres; we received 14 questionnaires back, with a total response rate of 48.3%. According to the type of healthcare provider, 15.4% were General Hospitals, 15.4% were Specialised Hospitals/Medical Schools, 30.8% were Private Clinics, 7.7% were Research Centres, and 30.8% were Health Centres. Geographically, the centres were dislocated as follows: 48% in the North, 28% in the Centre, 14% in the South, and 10% in the Islands.

Stratification of the treated cases per TNM classification showed that HIFU is usually performed on T1-T2 patients but not exclusively (some T3 patients have been treated also). However in 3 of the responding centres the population of T1-T2 patients has been split among different treatment options other than HIFU. The total number of procedures performed with HIFU stratified per centre showed that the treatment rate with HIFU on all the treatment options ranged from 14% to 40% in 2008 and from 5% to 69% in 2009. HIFU has been used as "first-line" treatment in 36.3% to 81.3% of the cases in 2008, and

in 57.1% to 100% of the cases in 2009. The stratification by age groups of patients treated with HIFU in 2008 and 2009 showed that treated patients were mainly in the age groups 71-75 and 76-80.

From the searches for economic studies no studies met our inclusion criteria.

Within the 29 centres, the HIFU system was purchased by 9 centres and rented by 17 centres; 3 centres did not provide this kind of information.

We estimated the cost per HIFU procedure by summing all the cost elements calculated within our assumptions: cost of the technology (rental), cost of the human resources involved (1 or 2 physicians, 1 or 2 nurses) and cost of drugs/materials/disposables used. We estimated a minimum total cost of € 2,938.60 and a maximum total cost of € 4,610.57 for the Ablatherm HIFU system. It was not possible to estimate the total cost for the Sonablate 500 HIFU system because the main cost elements were not available.

Due to lack of results from the literature search for economic studies it was not possible to match the data. For the comparison between the cost estimated and the DRG fees, we consulted the TUC 2009 (*Tariffa Unica Convenzionale*, Reimbursement fee from the Italian Ministry of Health) and we linked the HIFU procedure to the DRGs 306 and 307, respectively "Prostatectomy with complications" (€ 4,630.93) and "Prostatectomy without complications" (€ 2,868.85).

As our survey showed that in some cases the HIFU treatment is performed after the TURP procedure, we included the cost of TURP in the calculation of potential costs of the HIFU procedure. In particular the procedure is associated to DRGs 336 and 337, "Transuretral Prostatectomy with complications" (€ 3,574.32) and "Transuretral Prostatectomy without complications" (€ 2,717.82). Finally, linking the HIFU procedure with the TURP procedure, assuming the procedures are provided in two different admissions, its cost ranged from € 5,609.62 to € 8,242.30.

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We have not taken into account the costs associated with post-interventional pathway and complications of treatment that may require costly interventions in addition to impact on patient quality of life.

Discussion

Evidence from our systematic review did not allow us to make a final statement about the comparative effectiveness of HIFU ablation versus the other options. No RCTs or other comparative studies had been published at the time of our searches. None are available at the time of writing (20 July 2011). All the 23 included studies were non-comparative and we believe that the lack of trials is the main problem in the field of medical devices and surgical interventions assessment. However so far only non-comparative retrospective studies have been published reporting on large groups of patients for long follow-up periods.

Although our considerations are limited to our population of interest, patients with localised prostate cancer T1-T2; low or intermediate risk who are being treated with curative intent, we believe that they are relevant enough to guide policy decisions as these are the primary candidates for treatment according to the manufacturer's indications.

As the HIFU treatment purportedly confers advantages in domains related to quality of life and patient-related outcomes, associated to its minimally invasive nature, all future studies should take into account these domains and highlight them in a clearer fashion.

According to the latest EAU Guidelines HIFU is not considered as an alternative treatment for the localised treatment of prostate cancer but as an "experimental" treatment. However we suggest considering HIFU as an investigational treatment since the mechanisms of action and short term effectiveness are already known but long-term data are expected.

The Italian scenario showed a different approach to the collaboration and contribution on the national survey. In particular we have had a very low response rate from the southern areas.

Even if T1-T2 patients represent the main target population for the treatment, we noted that also T3 patients have been treated with HIFU and a fraction of T1-T2 patients received a different treatment option. A similar consideration can be made about the use of HIFU as "first-line" treatment: it has been used mainly as "first-line" but a part of patients (about 23% in 2009) received the treatment as non first-line (e.g. "second-line").

HIFU technology if widely used in Italy; Ablatherm is by far the most common and used HIFU system (used by all the centres with the exception of two that use Sonablate 500). Rental, which is offered only from the manufacturer's subsidiary of Ablaterm, is the most common type of acquisition of the technology (only 9 of the 29 centres purchased the HIFU system).

For a HIFU session, the typical staff is composed by: urologist, anaesthetist and one or two nurses; the procedure is performed within an operating theatre.

To our knowledge this is the first attempt at estimating the costs related to the HIFU procedure (no studies were identified by our searches). Our cost analysis showed that the estimated total cost of the HIFU procedure, assuming specific hypotheses (e.g. linking the reimbursement of the HIFU procedure to specific DRGs and considering only the rental of the HIFU system), has a similar value to the DRG fee linkable to such procedure (i.e. Prostatectomy), even though the DRG refers to a surgical intervention. It is very important to highlight that in about 60% of the surveyed cases, a TURP was needed concomitant to HIFU and this increases the final total cost.

It is essential to inform the patient properly. Some patients prefer maintaining their sexual function and quality of life rather than have a longer term survival after a curative approach. The ongoing trials should show soon if observational management is a good solution for prostate cancer.

In February 2011 the French National Authority for Health (HAS) granted Ablatherm HIFU treatment temporary reimbursement authorization under a special regimen for innovative therapies. In Italy a specific reimbursement fee for HIFU does not exist; however, given its diffusion in the whole country, this does not function as a disincentive.

Recommendations

We recommend performing HIFU ablation of localised prostate cancer in T1-T2 patients as an investigational treatment until comparative effectiveness will be generated. When evidence will be

available and support the use of the HIFU technology, we recommend defining strategies to gather all the related costs to plan proper HIFU-specific reimbursement fees.

1. Background

1.1 Clinical problem

Prostate cancer represents one of the most common cancers in men[1,2]. It is a complex disease of aging males, in which ethnicity and family history are related to the risk of developing the disease. The incidence of prostate cancer increases with age and is rare before 50 years of age[3].

Prostate cancer can be classified as localised, locally advanced, advanced (or metastatic), and hormone refractory[2,4]. Localised prostate cancer includes a tumour confined to the prostatic capsule or at most with an extraprostatic extension (T1 and T2 patients; extraprostatic extension is classified as T3 disease and would be considered locally advanced as opposed to localised), without spread to seminal vescicles or regional lymph nodes, and/or other organs. Locally advanced prostate cancer is defined as cancer that has spread beyond the prostate but has not yet metastasized to the lymph nodes, bones or other organs (T3-T4, N0, M0 patients). When the cancer is metastatic, the tumour has spread beyond the prostate gland to lymph nodes, bone or other organs (T, N1, M0, and any N, M1 patients). There is no universally accepted definition of hormone refractory prostate cancer. The disease can be considered to be hormone refractory when androgen withdrawal therapy or combined androgen blockade are no longer controlling the prostate-specific antigen (PSA) or the symptoms of the disease, or when there is radiological evidence of progression[2].

There are no typical symptoms of prostate cancer and, if present, they can be also similar to those of benign prostatic hyperplasia (BPH). The onset is asymptomatic in most cases. However, increased urinary frequency, weak urinary stream, urinary obstruction, lower urinary tract infections and inadequate bladder emptying may be found. Other symptoms may include erectile dysfunction and haematuria[2]. International epidemiological studies show an increased risk in the presence of familial cancer history related to the degree of kinship, the number of cases diagnosed within the family, and the early age of disease onset[2]. Other risk factors are: dietary and hormonal factors, lifestyle such as environmental exposures, tobacco smoking, and alcohol consumption[2].

The diagnosis of prostate cancer is established by transrectal ultrasound guided biopsy of the prostate which is typically prompted by an abnormality in the PSA blood test, digital rectal examination (DRE), or both. After diagnosis patients can be risk stratified using nomograms based on PSA at time of diagnosis, findings on rectal examination and features of the tumor on biopsy, most importantly the Gleason score.

1.2 Epidemiological data

In Europe the incidence rate of prostate cancer is 55 cases per 100,000 inhabitants and the mortality rate of 22.6 deaths per 100,000 people[1]. The age-standardised incidence rate of prostate cancer has increased in the last years in all cancers networks, as in England and Wales[2]. Data from the SEER

(American Surveillance, Epidemiology and End Results) and the PROCESS study (Prostate Cancer in Ethnic Subgroups) show that there is a 3-fold increase in the incidence of prostate cancer in black men compared to white men irrespective of the country of origin of the black man[5].

In Italy prostate cancer is the most common cancer in men with an estimated 36,500 new cases in 2008. The incidence, due to a widespread use of the PSA test, showed a marked increase in the late '80s whereas the mortality rate shows a stable trend after the marked increase in the '70s. The 5-years survival rate increased from 66% in 1990-1994 to 83% in 1995-1999[6].

As radical prostatectomy is solely performed for prostate cancer[3], we analysed the SDO database (hospital discharge records database held by the Italian Ministry of Health) to assess the number of radical prostatectomies performed in Italy, in particular DRGs for "Prostatectomy" with and without complications (306 and 307 respectively). We reported in Table 1.1 and Figure 1.1 the number of discharged patients (latest data available were for 2009)[7,8]. The age distribution is reported in Table 1.2 and in Figure 1.2 and 1.3 for both the DRGs analysed.

Table 1.1: Number of discharged patients for "Prostatectomy" (DRGs 306 and 307).

DRGs	2001	2005	2009
DRG 306 *Prostatectomy with complications*	1,292	1,237	1,140
DRG 307 *Prostatectomy without complications*	3,687	3,503	3,201
Total	**4,979**	**4,740**	**4,341**

Source: Data from SDO analysed by Agenas

Figure 1.1: Stratification of patients discharged for DRGs 306 and 307 in the years 2001, 2005 and 2009 (latest data available).

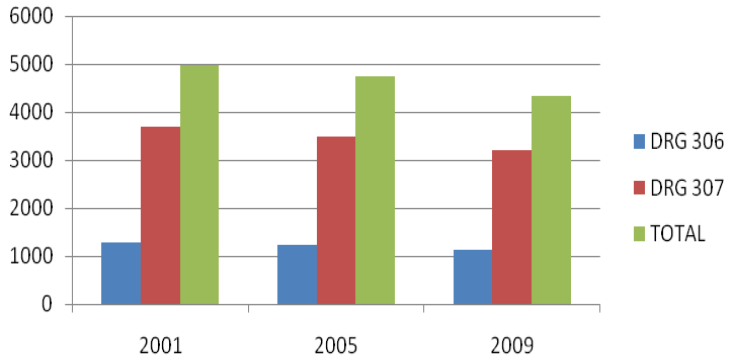
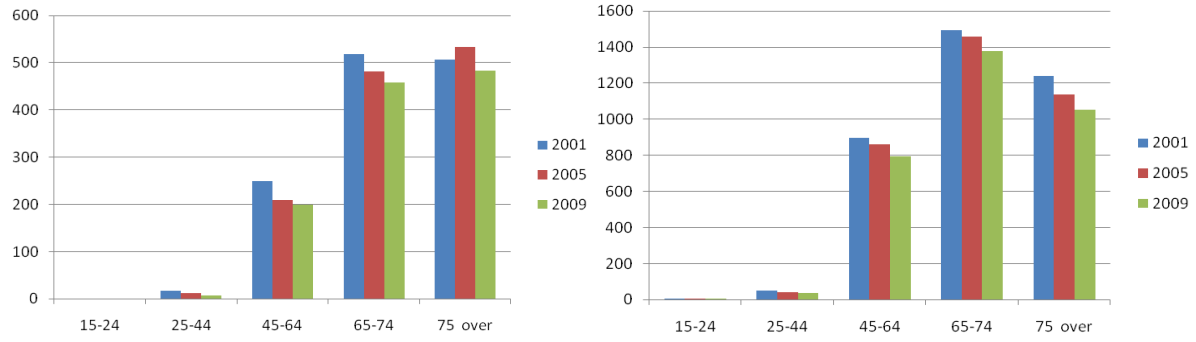


Table 1.2: Stratification of patients per age groups in the years 2001, 2005 and 2009 (latest data available).

Age group	DRGs	2001 [number of cases]	2005 [number of cases]	2009 [number of cases]
15-24	306	0	0	0
	307	4	3	5
25-44	306	18	12	8
	307	50	41	35
45-64	306	249	209	199
	307	897	860	796
65-74	306	518	482	458
	307	1,495	1,460	1,378
75 and over	306	507	533	484
	307	1,240	1,138	1,051
Total		**4,978**	**4,738**	**4,414**

Source: Data from SDO analysed by Agenas

Figure 1.2: Stratification of patients per age groups in the years 2001, 2005 and 2009 (latest data available) for DRG 306 (left) and DRG 307 (right).



1.3 Treatments and clinical pathways

We searched on the web and on the official websites of national and international institutions and organizations of professionals looking for guidelines. We intended to consider only the most recent documents.

We found the Guidelines of the European Association of Urology (EAU) on prostate cancer from the association's website (www.uroweb.org). We used the AGREE instrument to assess the guidelines[9]. Two appraisers (AM and MRP) independently assessed the guidelines. Scores for the six domains assessed are reported in Table 1.3. The overall assessment suggests recommending the guidelines highlighting the following minor methodological weaknesses: i) to consider more the patient's view during the guidelines elaboration process; ii) to involve external experts within the review process prior to the publication of the guidelines.

Table 1.3: The six independent domain scores calculated according to the AGREE instrument.

AGREE	
Scope and purpose	78%
Stakeholder involvement	58%
Rigour of development	81%
Clarity and presentation	75%
Applicability	39%
Editorial independence	100%

According to the latest EAU Guidelines on prostate cancer[4], prostate cancer patients with clinically localised disease (T1-T2) have the treatment options listed in Table 1.4 (Table A.1 in Appendix 1 for a brief description). For each option recommendations are reported and graded according to the available evidence:

- Grade A = *Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial;*
- Grade B = *Based on well-conducted clinical studies, but without randomised clinical trials;*
- Grade C = *Made despite the absence of directly applicable clinical studies of good quality.*

When considering treatment options, the patient, their family and physician must take into account his life expectancy (whether more or less than 10 years), his acceptance of the treatment-related complications, contraindications for surgery, and tumour differentiation grade. Options are mainly graded as "B" as most of the options are not supported by robust evidence, i.e. RCTs are lacking.

For patients with T1-T2 staging there are two options for the conservative management of cancer: Watchful Waiting and Active Surveillance: the main difference is that with Watchful Waiting the patient receives palliative treatments when symptoms progress whereas those on active surveillance may be treated by more definitive measures if there is evidence of progression while on surveillance. The Active Surveillance strategy thereby may allow patients to defer treatment until a time at which sexual and urinary side effects may be less bothersome. The surgical treatment of prostate cancer consists of Radical Prostatectomy; this option is the only graded as "A" by the EAU Guidelines. Radiotherapy, both by External Beam Radiation Therapy (EBRT) and Transperineal Brachytherapy, is also proposed to patients either not suitable, or not wishing surgery. Hormonal therapies are used when attenuation of symptoms are needed or in conjunction with radiotherapy for localised disease but are not considered curative when used independently.

Table 1.4: Therapeutic treatment options for primary prostate cancer (T1-T2) as indicated in the latest EAU Guidelines[4].

Stage	Treatment	Comment	Grade
T1a	Active Surveillance	Standard treatment for well-, and moderately, differentiated tumours and < 10-year life expectancy. In patients with > 10-year life expectancy, re-staging with TURP and biopsy is advised.	B
	Radical prostatectomy	Optional in young patients with a long life expectancy, especially for poorly differentiated tumours.	B
	Radiotherapy	Optional in younger patients with a long life expectancy, especially for poorly differentiated tumours. Higher complication risks after TURP, especially with interstitial radiation.	B
	Hormonal	Not an option	A
	Combination	Not an option	C
T1b-T2b	Active surveillance	Treatment option in patients with cT1c-cT2a, PSA < 10 ng/ml, biopsy Gleason score < 6, < 2 biopsies positive, < 50% cancer involvement of each biopsy. Patients with a life expectancy < 10 years. Patients who do not accept treatment-related complications.	B
	Radical prostatectomy	Standard treatment for patients with life expectancy > 10 years who accept treatment-related complications.	A
	Radiotherapy	Patients with a life expectancy > 10 years who accept treatment-related complications. Patients with contraindications for surgery. Unfit patients with 5-10 years of life expectancy and poorly differentiated tumours (combination therapy is recommended; see below).	B
	Brachytherapy	LDR brachytherapy can be considered in low risk prostate cancer, patients with a prostate volume < 50 ml and an IPSS < 12.	B
	Hormonal	Symptomatic patients, who need palliation of symptoms, unfit for curative treatment. Anti-androgens are associated with a poorer outcome compared to "watchful waiting" and are not recommended.	C
	Combination	For high-risk patients, NHT and concomitant hormonal therapy plus radiotherapy results in increased overall survival.	A

Adapted from Heidenreich A, Bolla M, Joniau S, Mason MD, Matveev V, Mottet N, Schmid H-P, van der Kwast TH, Wiegel T, Zattoni F. Guidelines on Prostate Cancer. European Association of Urology 2010. (www.uroweb.org).

Key: TURP = transurethral resection of the prostate; LDR = low-dose rate; IPSS = International Prostatic Symptom Score; NHT = neoadjuvant hormonal treatment.

2. Technology, procedure and alternatives

2.1 Technology and procedure description

HIFU (High Intensity Focused Ultrasound) ablation represents a new treatment for prostate cancer management[10]. HIFU destroys tissues by a thermal and mechanical effect. The thermal effects result in ultrasound energy absorbed into the tissue and converted into heat (target tissue can reaches 80-100 ºC), causing tissue damage through coagulative necrosis. The mechanical effects result from the negative pressure of the ultrasound wave causing bubbles to form inside the cells (cavitation), which increase in size until they suddenly collapse, which causes damage to nearby cells[11].

The main elements of an HIFU system are: the endorectal probe that encloses a piezoelectric or piezoceramic transducer to generate ultrasound waves which are focused into a focal point by a concave or parabolic configuration and an ultrasound scanner for treatment planning; the visualisation system, i.e. the monitor that allows to set and control the treatment procedure through echographic screening[12]. In our preliminary searches on the General Repertory of medical devices marketed in Italy (RDM) managed by the Italian Ministry of Health[13], we identified two commercial HIFU systems for prostate cancer management: the Ablatherm® HIFU (manufactured by EDAP-Technomed®) and the Sonablate 500® (manufactured by Focus Surgery®). A summary of usage, costs and clinical data supporting either system as well as the organisational implications of the utilisation of the technologies are included within the objectives of this HTA report.

HIFU treatment is generally administered transrectally using local, regional or general anaesthesia. Generally, a refrigeration system (e.g. a cooling balloon surrounding the probe) protects the rectal mucosa. The procedure can be repeated over time and can be performed in day-surgery, outpatient or inpatient settings. HIFU may be preceded by a TURP (transurethral resection of the prostate)[14]. The latter is intended to allow a faster recovery due to the facilitation of urination postoperatively, reduction of the volume of necrotic tissue that will be present, to remove calcifications (which could interfere with ultrasound transmission), and to reduce the prostate gland to 24 mm in diameter (so that the entire gland can be treated)[15]. This protocol may allow the complete treatment in a single session[11].

2.2 Regulatory status of the technology

Ablatherm® and Sonablate 500® received the CE mark in 2000 and 2001 respectively so they can be clinically used in Europe.

Approval for clinical use by the FDA has not been received yet either from Ablatherm® and Sonablate 500® so these systems can be used in the United States only under an IDE (Investigational Device Exemption); it means that they can be used only within a phase III multicentric clinical study to collect data (on both effectiveness and safety) for the final FDA approval[14].

2.3 Alternative therapies

HIFU ablation is proposed as alternative to the following standard treatments of localised prostate cancer in primary therapy:

- Active Surveillance: to select and treat only patients with aggressive tumours, eligible for radical treatments, with life expectancy exceeding 10 years and a low risk of disease progression who refuse urgent treatment[16,17];
- Watchful Waiting: to select patients for non-aggressive treatments only when they become symptomatic and life expectancy is less than 10 years[16,17];
- Radical Prostatectomy: surgical procedure, performed under general or regional anaesthesia to remove the whole prostate gland as well as the surrounding tissue;
- Radiotherapy (external): also known as EBRT (external beam radiotherapy) is the treatment of prostate cancer by radiation with different doses and irradiation techniques;
- Hormone therapy: based on the removal and/or blockage of hormonal effects that stimulate the growth of prostate cancer cells. Can be performed by the suppression of the secretion of testicular androgen, by pharmacological or surgical castration, or by inhibition of the androgen receptors in prostate cells action[17].

In other countries HIFU is also proposed as an option for salvage therapy (locally proven recurrence of prostate cancer after external radiation or brachytherapy failures). HIFU is an alternative to the following curative salvage treatment options:

- salvage radiotherapy, after radical prostatectomy failure;
- salvage prostatectomy, brachytherapy and cryosurgery after radiotherapy failure.

There is no definitive evidence for the superiority of any one treatment over the others and the merits and risks of each are still debated. The best treatment is related to the patient's age, his health status, the cancer stage and the personal preference[2,18].

3. Report's objectives: policy and research questions

Objectives of this HTA report are the following:

- To assess and analyse effectiveness and safety data from the scientific literature on the HIFU treatment of localised prostate cancer compared to standard treatments;
- To describe the level of adoption and utilisation of the technology within the providers of the Italian NHS and to investigate the availability of (non-frequent) alternative treatment options;
- To perform an economic analysis on the utilisation of the technology within the Italian clinical practice;
- To assess patient acceptability of the HIFU treatment.

Policy question

Based on available evidence, is it possible to provide guidance on the use of HIFU for the treatment of localised prostate cancer within the Italian NHS?

Research questions

- What is the evidence of effectiveness and safety of the technology versus the standard treatments?
- What is the level of adoption and use of the technology by healthcare providers of the Italian NHS?
- On the basis of evidence, is the use of the technology appropriate for the specific condition identified?
- What is the economic impact of using the technology versus the standard treatments for prostate cancer?
- What training or organizational changes may be required to establish new HIFU programs?
- What are the aspects that may interfere with the patient's acceptability?

4. Assessing the evidence

4.1 Methods

We carried out searches of the available evidence from both primary and secondary literature, to identify and assess the effectiveness and safety of HIFU treatment for prostate cancer compared to alternative treatments in the target population, i.e. males with localised prostate cancer (T1-T2), with low or intermediate risk disease who are being treated with curative intent. Citations have been managed by ProCite, Version 5 (Windows 2000/98/95NT and Power Macintosh). Selection of the studies (by reading of title and abstract) was performed in double (AM and TJ); eligible studies were analysed in full text; studies met inclusion criteria were extracted in double. Disagreements were solved by consultation of a third author (MRP).

Secondary literature

Searches for secondary literature were run on the Cochrane Database of Systematic Review and on the CRD database. In particular, we accessed the DARE (Database of Abstracts of Reviews of Effects) and the HTA Database to identify systematic reviews and HTA reports respectively. We intended to consider any document published in English or Italian from 1st January 2000 to 6th October 2010 (see Appendix 2 for search strategy, results and excluded studies).

Primary literature

Systematic searches for primary literature were run on three main databases: EMBASE, Cochrane Library and Medline. We intended to identify comparative clinical studies but we considered to include also observational case series whether comparative studies were not available. We included studies assessing the HIFU treatment and published in English or Italian from 1st January 2000 to 17th December 2010. Excluded studies were listed together with reasons for exclusion (see Appendix 3 for search strategy, results and excluded studies).

Other sources

We intended to consider also information from *"gray literature"* (conference proceedings, websites, ongoing clinical studies, unpublished work, and data from national and international registries). We identified the manufacturer's subsidiary for Ablatherm (EDAP Technomed Italia Srl) and the distributors for Sonablate 500 (Alliance Medical Srl) and run searches on their websites.

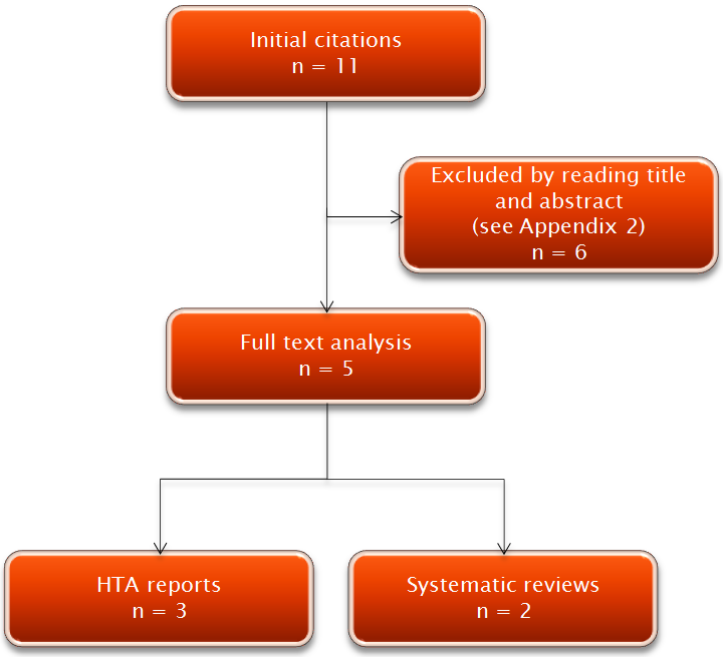
4.2 Results of literature review

Secondary literature review

We found eleven citations (Figure 4.1). Six citations were excluded by reading title and abstract (see Appendix 2). Five citations were considered relevant for a full text analysis: three were assessment documents produced by HTA agencies[14,19,20]; two were systematic reviews[18,21]. According to our research protocol, we decided to update the latest systematic review with the most recent evidence. Such review

was by Warmuth et al. [21] and we decided to use it as our evidence base and update the searches to 17th December 2010.

Figure 4.1: Flow diagram of literature search for secondary literature.



Primary literature review

In our systematic review we included (Figure 4.2):

- studies included in the review by Warmuth et al.[21] that met our inclusion criteria;
- studies meeting our inclusion criteria published from 1st January 2000 to 17th December 2010.

The studies from the review by Warmuth et al.[21] were eighteen[10,22–38]. We excluded one study as it was in German[38]; this left 17 studies.

We did not find any study published after the review by Warmuth et al.[21] to update evidence. However we were able to find and include 6 studies[12,39–43] that were previously excluded by Warmuth et al.[21] as they reported on populations of less than 50 patients.

We carried out the data extraction from the 23 studies using 2 evidence tables reporting: Study details, Population and follow-up, and Procedure details (Table 4.1) and Outcomes, Quality of life and patient-related outcomes, and Adverse events (Table 4.2). The 23 studies we included were all observational case series. No RCTs or comparative studies were found.

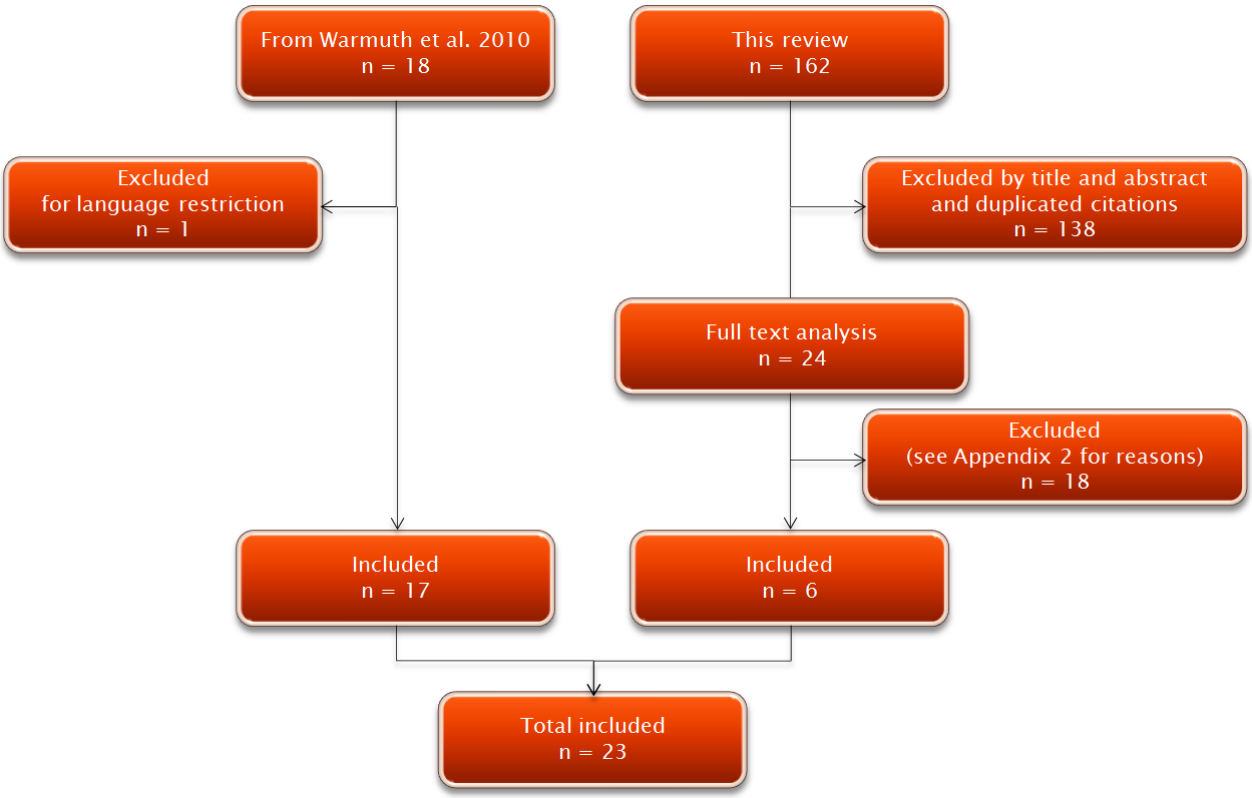
Referring to Table 4.1: population within the studies ranged from 19 to 517 patients: 6 studies presented results on less than 50 patients; 5 studies reported results on a population between 50 and 100 patients; 12 studies presented results on populations with more than 100 patients. Mean age was more than 70 years in most of the studies. All the included studies presented limited mean follow-up periods; the

longer follow-up was in the study by Blana et al. 2008[23] with 77 ± 12 months of mean follow-up. The Ablatherm HIFU system was used in 13 studies (1,920 patients) and the Sonablate 500 HIFU system was used in 10 studies (1,311 patients). In some cases prototypes or old versions of both the HIFU systems have been used and this limits the generalisability of results.

Ten of the 23 studies reported whether TURP was performed before or concomitant to HIFU procedure (in 7 studies TURP was performed in more that 65% of the patients; in 3 studies TURP was not performed at all); no information about TURP were reported in 13 studies.

Eighteen of the 23 studies reported whether neoadjuvant androgen-deprivation therapy (ADT) was administrated to patients; frequency was from 0% (6 studies) to 66% (1 study). No information about neoadjuvant ADT was reported in 5 studies.

Figure 4.2: Flow diagram of literature search for primary studies.



Biochemical disease-free survival rate (as mean PSA nadir or PSA level at final follow-up visit) was reported in all the studies but one as well as negative biopsy rate (not reported in 4 studies) (Table 4.2). Overall survival rate, as well as prostate cancer-specific survival rate, was generally not reported (only in 5 and 7 studies respectively); this likely relates to the short follow-up periods of all the studies and the long natural history of clinically localised prostate cancer. Quality of life and patient-related outcomes as well as functional assessment of urinary flow, were assessed in 7 studies: they reported score from IPSS and IPSS-QoL, UCLA-PCI, FACT, and Q-max.

All the studies reported in detail the adverse events related to urinary tract and rectum while pain was not often reported. The analysis of the sexual potency was performed pre- and post-operatively in many of the studies (18 studies).

The safety profile of the HIFU treatment can be summarised taking account of:

- Occurrence of rectourethral fistula: in up to 20% of patients treated[43]; however, this is elevated by a high fistula rate in a study of 20 patients; larger studies showed lower incidence (e.g. 1.2% on 402 patients treated with Ablatherm[32] and 0.9% on 517 patients treated with Sonablate 500[36]);
- Occurrence of adverse events related to the urinary tract: urethral stenosis or obstruction, and infections are the most common (up to 60%[27] and 58%[25] of the patients treated respectively); different grades of urinary incontinence have been reported in up to 24% of the patients treated[25].

4.3 Discussion on clinical evidence

Our systematic review added little to the review by Warmuth et al.[21]. We were able to find and include just studies reporting results from small groups of patients. No RCTs or other comparative studies had been published at time of our searches.

We believe that the design of the studies is the main problem. This is a common issue in the field of medical devices and surgical interventions assessment[44]. All the studies published at time of writing are of course useful to identify procedure-related safety, even at medium- to long-term, but they can't provide relatively unbiased information on comparative effectiveness. It is not possible to assess if HIFU treatment is more effective than Active Surveillance, Radical Prostatectomy, Radiotherapy, or LDR Brachytherapy in the population considered. Moreover, within the latest EAU Guidelines[4] HIFU is considered an experimental treatment for the local treatment of prostate cancer. The guidelines state that longer follow-up is mandatory to assess its true role in the management of prostate cancer patients.

Further, as the HIFU treatment supposedly confers advantages (associated to its less invasiveness and energy source) to domains related to quality of life and patient-related outcomes, these should be assessed and highlighted in a more evident fashion.

According to our systematic review, the evidence available at December 2010 is not sufficient to give evidence based indications on the use of HIFU for localised prostate cancer. Although our considerations are limited to our population of interest, patients with localised prostate cancer T1-T2; low or intermediate risk who are being treated with curative intent, we believe that they are relevant enough to guide policy decisions as these are the primary candidates for treatment according to the manufacturer's indications.

Table 4.1: Evidence table reporting study details, population, follow-up, and procedure details from the 23 included studies.

Study details		Population and follow-up				Procedure details		
Study [ref.]	**Country**	**N. of patients**	**Age (range) [years]**	**Tumor stage [TNM]**	**Follow-up (range) [months]**	**HIFU system**	**TURP [% of patients]**	**Neoadjuvant ADT [% of patients]**
Ahmed, 2009 [22]	UK	172	mean = 64 ± 8 (47-88)	≤ T1c-T3bN0M0	mean = 12 ± 8 (5-25)	Sonablate	0	29%
Blana, 2004 [24]	DE	146	mean = 70 ± 7	T1-T2N0M0	mean = 23 (4-62)	Ablatherm	NR	43%
Blana, 2008 [23]	DE, FR	140	median = 70 (45-87)	T1a-T2cNxM0	mean = 77 ± 12	Ablatherm	NR	16%
Challacombe, 2009 [39]	UK	28	mean = 70.1 (60–79)	D'Amico low-, intermediate- and high-risk	24.9 (± 4.9) months	Ablatherm	100%	36%
Chaussy, 2000 [27]	DE	65	NR	Localised	mean = 10 (1-18)	Ablatherm	NR	NR
Chaussy, 2001 [25]	DE	184	mean = 72 (59-81)	T1-T2NxM0	mean = 6; median = 4 (0-30)	Ablatherm	NR	NR
Chaussy, 2003 [26]	DE	271 A = 96 HIFU B = 175 TURP + HIFU	mean A = 66 ± 8; mean B = 68 ± 7;	T1-T2c	mean A = 19 ± 12; mean B = 11 ± 6;	Ablatherm	65%	NR
Colombel, 2006 [37]	FR	242	mean = 71 ± 6	T1c-T2	NA	Ablatherm	100%	NR
Gelet, 2001 [10]	FR	102	mean = 71 ± 6	T1b-T2	mean = 19 (3-76)	Ablatherm	NR	8%
Illing, 2006 [41]	UK	34 group 1 (automatic) = 9 group 2 (visually) = 25	mean: group 1 = 64 (53–75) group 2 = 61 (50–76)	≤ T2 (N0,M0)	minimum = 3 months	Sonablate	NR	0%
Koch, 2007 [40]	US	19	NR	T1–T2	6 months	Sonablate	NR	NR
Lee, 2006 [28]	KR	58	mean = 70 ± 6	T1-T2	mean = 14 ± 4	Ablatherm	91%	29%
Maestroni, 2008 [12]	IT	25	mean = 71.6 (56-78)	From T1-T2a to T2c	6 months	Ablatherm	100%	40%
Mearini, 2009 [29]	IT	163	median* = 72 (68-75)	T1c-T3aN0M0	median = 24 (12-41)	Sonablate	0%	0%
Muto, 2008 [30]	JP	70 (41 full; 29 focal)	median = 72 (61-80)	T1c-T2N0M1	median = 34 (8-45)	Sonablate	NR	34%
Poissonnier, 2007 [31]	FR	227	mean = 69 ± 6	T1-T2	mean = 28 ± 20; median = 21 (12-107)	Ablatherm	78%	33%
Thüroff, 2003 [32]	DE, FR, NL	402	mean = 70 ± 7	T1-T2N0-NxM0	mean = 14 (0-51)	Ablatherm	NR	0%
Uchida, 2002 [43]	JP	20	mean = 72.2 (57-86)	T1b-2N0M0	mean = 13.5 ± 6.8 (6-31)	Sonablate	NR	20%
Uchida, 2005 [33]	JP	72	median = 72 (45-79)	T1c-T2bN0M0	median = 14 (2-24)	Sonablate	NR	0%
Uchida, 2006 [34]	JP	63	median = 71 (45-87)	T1c-T2bN0M0	median = 22 (3-63)	Sonablate	0%	0%
Uchida, 2006 [35]	JP	181	median = 70 (45-88)	T1c-T2bN0M0	median = 18 (4-68)	Sonablate	NR	52%
Uchida, 2009 [39]	JP	517	median = 68 (45-88)	T1c-T3N0M0	median = 24 (2-88)	Sonablate	NR	66%
Vallancien, 2004 [42]	FR	30	mean = 72 (61-79)	Localised PCa	median = 20 (3-38)	Ablatherm	73%	0%

Key: N. = number; HIFU = high intensity focused ultrasound; TURP = trans-urethral resection of the prostate; ADT = androgen deprivation therapy; NR = not reported; UK = United Kingdom; DE = Germany; FR = France; US = United States of America; KR = South Korea; JP = Japan; IT = Italy; NL = the Netherlands.

Table 4.2: Evidence table reporting on biochemical, histological, quality of life and patient-related outcomes, and adverse events from the 23 included studies.

Study, Year [ref.]	Outcomes				Quality of life and patient-related outcomes	Adverse events related to:			
	Biochemical disease-free survival rate	Negative biopsy rate	Overall survival rate	PCa specific survival rate		Urinary tract	Rectum	Sexual potency	Pain
Ahmed, 2009 [22]	@ 12 months 78.3% achieved a PSA nadir ≤ 0.5 ng/ml	NR	NR	In 92.4% no evidence of disease (PSA < 0.5 ng/ml or negative biopsy if nadir not achieved)	NR	Urethral stricture in 19.4 to 40.4% Infection in 23.8% Epididymitis in 7.6% Mild stress urinary incontinence in 7.0%	None noted	Potency maintained in 70%	NR
Blana, 2004 [24]	Of the 137 patients with complete follow-up: 56% had a PSA nadir of less than 0.1 ng/mL 83% less than 0.5 ng/mL and 92% less than 1 ng/mL @ 22 months median PSA was: 0.15 ng/mL (0-12.11). 87% of all patients had constant PSA levels of less than 1 ng/mL	93.4% (of 137) showed constant negative control biopsies.	NR	NR	IPSS and Quality of Life Index did not change from before to after treatment.	Infravesical obstruction in 11.7% Symptomatic infection in 4.8% No severe stress incontinence was observed.	1 rectourethral fistula after a second HIFU treatment.	Erectile function was preserved in 47.3% of patients.	NR
Blana, 2008 [23]	@ 4.9 months median PSA nadir was 0.16 ng/ml (0.0-9.1) PSA nadir of 0.5 ng/ml in 68.4% of patients.	Negative control biopsies in 86.4% of patients.	90% at 5 years; 83% at 8 years.	100% at 5 years; 98% at 8 years.	NR	Incontinence grade I in 5% Infection in 7.1% Urinary obstruction in 13.6%	None noted	On 100 previously potent patients: 56.8% were potent; 17.3% were partially impotent; 25.9% were totally impotent.	Pelvic in 5.7%
Challacombe, 2009 [39]	PSA nadir was 1.3 (± 2.7) ng/mL	Biopsy = 80% positive Phoenix = 46% FDA = 75%	100%	100%	NR	Urinary retention = 1% Urethral stricture = 2% Prostatitis = 0%	Urorectal fistula = 0%	Erectile function: 50% had SHIM score ≥ 21	NR
Chaussy, 2000 [27]	PSA nadir <4 ng/mL in 69% and 91% of the patients after selective and complete HIFU treatment.	65% (selective); 83% (complete).	NR	100%	NR	Urinary obstruction in 60% Urethral lesion with stenosis; Stress incontinence.	Rectourethral fistula.	NR	NR
Chaussy, 2001 [25]	PSA nadir < 4 ng/mL in 97% < 0.5 ng/mL in 61%	80%	NR	NR	QoL did not change significantly (from 1.8 to 2.1 on a 6-point scale). The IPSS changed from 5 to 4.	Infections in 58% to 17% Mild stress incontinence in 24% to 3.9%	Rectourethral fistulas in 3.1% to 0.5%	Potency was preserved in one third of the men when the entire prostate was treated.	NR

Chaussy, 2003 [26]	@ 15 weeks (avg) mean PSA nadir HIFU: 0.48 ng/mL (±1.10) TURP + HIFU: 0.26 ng/mL (± 0.90)	HIFU = 87.7% TURP + HIFU = 81.6%	NR	NR	IPSS @ 3 months: HIFU = from 6.47 to 8.91 (mean values); TURP + HIFU = from 6.69 to 3.37 (mean values). IPSS-QoL: HIFU = from 1.30 to 2.36 TURP + HIFU = from 2.05 to 1.86	Incontinence: HIFU = 9.1% grade 1 and 6.3% grade 2; TURP + HIFU = 4.6% grade 1 and 2.3% grade 2. Infections: HIFU = 47.9%; TURP + HIFU = 11.4%. Urinary obstructions: HIFU = 27.1%; TURP + HIFU = 8%.	NR	No changes: HIFU = 60%; TURP + HIFU = 68.2%	NR
Colombel, 2006 [37]	@ 3 months median PSA nadir 0.1 ng/ml	@ 3 months = 87%	NR	NR	NR	Sloughing of necrotic tissue = 4% Bladder-neck stenosis = 12–16% Urinary incontinence (grade 1) = 5.8–9.5%	NR	No nerve-sparing = 30% potent (IIEF) Nerve-sparing = 40–60% potent (IIEF)	Pelvic perineal in 1–2%
Gelet, 2001 [10]	NR	@ final follow-up 75% were cancer-free	NR	NR	NR	Stress incontinence grade 1 = 8.8% Stress incontinence grade 2 = 9.8% Stress incontinence grade 3 = 3.9% Retention = 4.9% Symptomatic infection = 7.8% Stenosis = 16.7%	Retrourethral fistula = 0.98%	25 of the 41 potent patients lost potency	Perineal in 1.96%
Illing, 2006 [41]	@ 3 months mean PSA nadir: group 1 = 1.51 ng/mL group 2 = 0.15 ng/mL (P<0.005)	NR	NR	NR	NR	Infection = 1/9 (group 1); 8% group 2; Epididymo-orchitis = 0/9 (group 1); 4% group 2	NR	NR	NR
Koch, 2007 [40]	@ 6 months PSA < 0.5 ng/ml in 42%	@ 6 months = 68%	NR	NR	NR	Bladder stone = 5% Bladder spasm = 5% Dysuria = 15% Epididymitis = 5% Gross hematuria = 15% Perineal discomfort = 5% Urinary incontinence = 20% Urinary retention = 10% Urinary tract infection = 40%	Anal discomfort = 5% Rectourethral fistula = 5%	NR	NR
Lee, 2006 [28]	@ 3 months PSA < 0.5 ng/ml in 78% (45/58) median PSA nadir 0.2 ng/ml (0.01-7.60)	NR	NR	NR	NR	Grade 1 stress urinary incontinence in 16%; Delayed passage of necrotic debris in 14%; Urethral stricture in 6.9%; Acute urinary retention in 3.4% patients.	NR	NR	NR
Maestroni, 2008 [12]	@ 6 months PSA from 0.4 ng/mL to 10.1 ng/mL	84% (from 94,2 % in the low risk group to 0% in the high risk group).	100%	NR	IPSS: from 8.4 (2-23) to 5.2 (1-14) pre- and post-op. QoL index: from 2.2 (0-4) to 1.7 (0-4) pre- and post-op.	Lower urinary tract symptoms = 12% Urge-incontinence = 12% Stress-incontinence = 0% Urethral stenosis = 0% Acute retention of urine = 8%	Recto-vesical fistula in 1 patient	All the 3 potent patients (IIEF-5) lost potency.	Perineal in 20%

Mearini, 2009 [29]	@ 2.3 months median PSA nadir 0.15 ng/ml (0.05-0.59) PSA nadir ≤ 0.4 ng/ml in 70.2% 78.1% were biochemically disease-free during follow-up.	@ 6 months positive prostate biopsy rate was 33.9% (after single treatment).	NR	NR	NR	Mild mixed urinary incontinence in 16%; Urethral stricture in 15%.	Rectal fistula in 0.6%	Median postoperative IIEF-5 score was 12 (6-20).	NR
Muto, 2008 [30]	@ 2 years 85.9% (in low), 50.9% (in interm.), 0% (in high risk).	@ 6 months 88.1% @ 1 year 81.6%	100%	100%	Both focal and whole therapy groups have shown that HIFU did not affect the UCLA-PCI and IPSS scores.	Urethral stricture = 8.6% and 4.0%; Symptomatic infection = 11.4% to 4.0%; Continence maintained in 49/52 patients; Urinary retention = 5.7%	NR	NR	NR
Poissonnier, 2007 [31]	@ 6 months mean PSA nadir 0.33 ± 0.70 ng/ml (median 0.10 ng/ml)	@ 3 months 86%	3%	66 % at 5 years.	NR	Incontinence = 13%; Stenosis = 12%; Sloughing = 9%; Urgency 5%; Acute infection 2%; Hematuria 0.5%	NR	Assessed on 67 patients only. 39% of the potent patients lost potency; With the nerve-sparing procedure, erections were preserved in 18 (69%) of 26 potent patients.	Perineal in 3%
Thüroff, 2003 [32]	@ 5.45 months mean PSA nadir 1.8 ng/ml (median 0.6 ng/ml)	@ 13.3 months 87.2%	NR	NR	NR	Stress incontinence grade 1 = 10.6% Stress incontinence grade 2 = 2.5% Stress incontinence grade 3 = 1.5% Infection = 13.8% Prolonged retention = 8.6% Presented urethral stenosis 3.6%	Urethrorectal fistula in 5 patients.	35 patients spontaneously reported partial or total loss of potency.	NR
Uchida, 2002 [43]	PSA nadir < 0.50 ng/mL in 65% PSA nadir from 0.50 to 1.00 ng/mL in 25% PSA nadir from 1.01 to 2.00 ng/mL in 10%	100%	NR	NR	NR	Urethral stricture = 10% Retention = 5%	Rectourethral fistula = 5%	30% of the potent patients lost potency.	NR
Uchida, 2005 [33]	@ 1 year 78% (60 patients only) @ 2 years 76% (60 patients only)	@ 6 months 68%	NR	NR	No differences in IPSS, Q-max, and FACT.	Urethral stricture = 18% Epididymitis = 8.3% Prostatitis = 5.6%	NR	39% of the potent patients lost potency.	NR
Uchida, 2006 [34]	Overall = 75%	@ final follow-up 87% were cancer-free.	NR	NR	NR	Urethral stricture = 24% Retrograde ejaculation = 3% Epididymitis = 3% Retention = 2% Stress incontinence grade 1 = 2%	Recto-urethral fistula = 2%	Erectile dysfunction: 25% of the 34 potent patients.	NR
Uchida, 2006 [35]	@ 1 year = 84% @ 3 years = 80% @ 5 years = 78%	NR	NR	NR	NR	Urethral stricture = 22% Epididymitis = 6%	Rectourethral fistula = 1%	20% of potent patients without NADT had erectile dysfunction. 9% of potent patients had retrograde ejaculation.	NR

Uchida, 2009 [39]	@ 5 years = 72%	83%	NR	100%	NR	Urethral stricture = 16.6% Urinary retention = 13.2 Epididymitis = 4.4% Incontinence (grade 1) = 0.8% Bladder neck contracture = 0.6% Hematospermia = 0.3% Perineal edema = 0.3%	Recto-urethral fistula = 0.9	Erectile dysfunction = 28.9% Retrograde ejaculation = 20.3%	NR
Vallancien, 2004 [42]	@ 1 year mean PSA 0.9 ng/ml (0.0-2.6)	@ 1 year = 73.3%	NR	NR	IPSS-QoL (from 0: delighted to 6: terrible): Mean score was from 2.4 to 1.6 pre and post. After treatment 12% of the patients were unsatisfied with quality of life (score 4 or greater) vs 37% before treatment.	Urinary retention = 6% Infection = 10% Hematuria = 66% Incontinence = 3%	Prostatorectal fistula = 0% Fecal incontinence = 0%	On the 14 potent patients: 11 partially lost potency; 5 were impotent. In total sexual function decreased in 32%	Anal in 0%

Key: NR = not reported.

5. Context analysis

5.1 Introduction to context analysis

Context analysis is crucial in the assessment of a health technology because it allows to identify its use and costs for the health care provider of that region. The aim of this chapter is to assess how the technology is used by the Italian NHS healthcare providers, for which health problems (indications), and what the associated costs are. We carried out a survey in the centres of the Italian NHS that perform HIFU ablation of prostate cancer. The rationale of such context analysis was to offer an impact scenario of the use of the HIFU technology in patients with localised prostate cancer.

5.2 Methods

To obtain data on the HIFU procedures performed in our context we followed two approaches: to search in the SDO database and to carry out a national survey by the healthcare providers.

The SDO database provides data on discharge for a specific diagnosis through the DRG system. From a preliminary analysis we noted that a specific DRG for the HIFU procedure does not exist; the only linkable DRGs were those related to "Prostatectomy". This information was confirmed by consultation with clinical experts.

The national survey was aimed to get all the relevant information on the use of the technology; we decided to build a structured questionnaire to collect data on the number of procedures performed in the centres that use the HIFU technology, on the clinical pathways followed, on the acquisition of the technology, and on the costs.

We identified all the centres providing the HIFU treatment for prostate cancer by searching on the manufacturers' website (www.edap-tms.com; www.focus-surgery.com) and also directly contacting the manufacturer's subsidiary for the Ablatherm HIFU system (EDAP Technomed Italia Srl).

We were interested in collecting data for 2008 and 2009. The survey was conducted by the Department of Urology of each centre identified. The questionnaire, sent by e-mail, was structured in 3 parts (see Appendix 4).

- ***Part 1 of 3: Healthcare provider and contacts***

  General information on the type of healthcare provider, details and contacts of the professionals in charge to fill out the questionnaire, as well as details of the head of department.

- ***Part 2 of 3: Population and clinical pathways***

  Information on the patients diagnosed of prostate cancer and treated, stratification per age groups, stratification of treated patients according to TNM classification as well as all the treatment options.

- ***Part 3 of 3***

  This part was divided in four specific sub-sections: the analysis of data from sub-section a) will be presented in this Chapter while data from sub-sections b), c), and d) will be presented and discussed in Chapter 6:

  a) Case records and details about the HIFU treatment: Information focused on HIFU patients such as type of hospitalisation, first-line treatment, number of HIFU sessions, stratification per age groups and TNM, number of patients who underwent TURP (trans-urethral resection of prostate) before the HIFU treatment, intra-procedural complications;

  b) Equipment: Technical as well as economic information on the HIFU system used, its related costs, professional training needed;

  c) Human resources used for the HIFU procedure: Information on the professionals involved in the procedure by type and time spent;

  d) Other resources used for the HIFU procedure: Information on the setting of the procedure and the disposables and drugs used (volumes and costs).

5.3 Results

From the SDO database analysis we processed data from DRG 306 ("Prostatectomy with complications") and DRG 307 ("Prostatectomy without complications"). Data stratified per age groups, from 1999 to 2009 (latest available data) have been previously presented (see Chapter 1).

The survey sample was represented by 29 centres that, within the Italian NHS, provide HIFU treatment (using one of the systems identified i.e., Ablatherm or Sonablate 500). The centres using Sonablate 500 were identified from the manufacturer's website; the centres using Ablatherm were identified by directly contacting the manufacturer's subsidiaries in Italy (see Chapter 2).

5.3.1 Healthcare provider and contacts (part 1 of 3 of the questionnaire)

Questionnaires have been sent to 29 centres (Appendix 5); we received 14 questionnaires back (Appendix 6), with a total response rate of 48.3%. Response rate per geographic area varied between 57% of the centres contacted in the North, and 75% of the centres contacted in the Centre; none of the centres contacted in the South and in the Islands sent the questionnaire back (Figure 5.1). All the centres were public or private NHS-accredited providers (Table 5.1). According to the type of healthcare provider, 15.4% of the centres providing HIFU were General Hospitals, 15.4% were Specialised Hospitals/Medical Schools, 30.8% were Private Clinics, 7.7% were Research Centres, and 30.8% were Health Centres. Geographically, the centres were dislocated as follows: 48% in the North, 28% in the Centre, 14% in the South, and 10% in the Islands.

Data for 2008 were provided by 6 of the 14 responding centres (42.9%) while data for 2009 were provided by 13 of the 14 responding centres (92.9%). The low response rate for 2008 can be explained considering that some centres had no data available for that year and/or were not using the technology

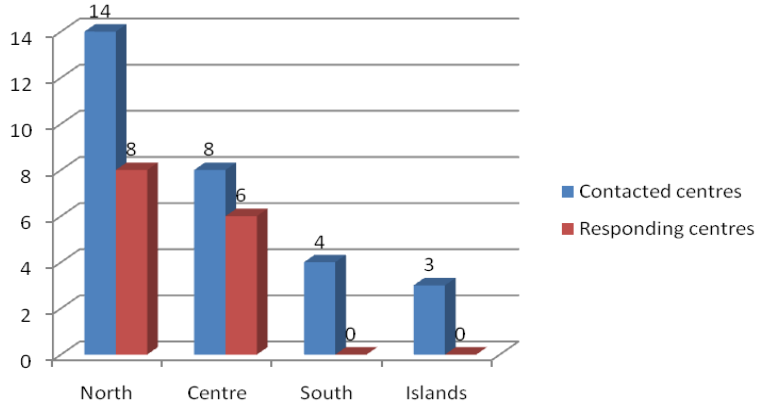
at that time. One of the responding centre started to use the HIFU technology in 2010 hence no data for 2008 and 2009 were available.

Table 5.1: Number and type of the responding centres (2008-2009).

Type of healthcare provider	Total number contacted	Total number responding
General Hospital	4	2
Specialised Hospital/Medical School	6	3
Private Clinic	7	4
Research Hospital	1	1
Health Centre	11	4
Total	**29**	**14**

Source: Data from survey analysed by Agenas

Figure 5.1: Geographical distribution of contacted and responding centres



Source: Data from survey analysed by Agenas

5.3.2 Population and clinical pathways (part 2 of 3 of the questionnaire)

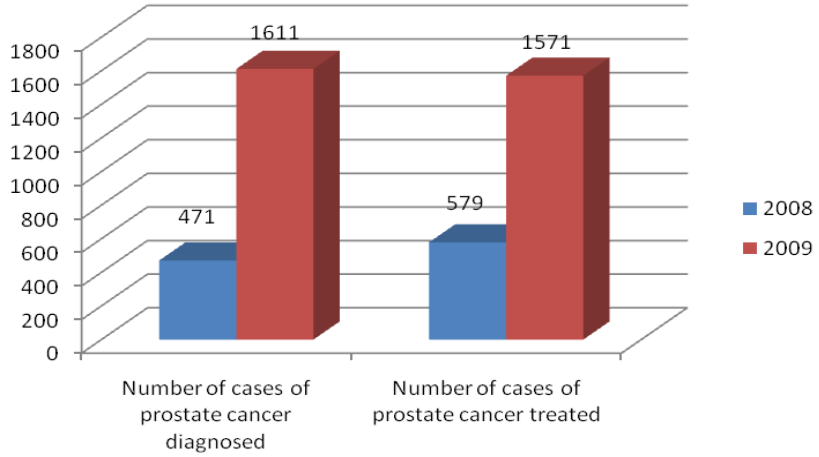
Data on the number of patients diagnosed and treated within the responding centres are reported in Figure 5.2 for both the years 2008 and 2009. It is important to highlight that for 2008 some centres provided only data on treated cases, so this could explain the difference between the number of patients treated (higher) and the number of patients diagnosed of prostate cancer.

The stratification of diagnosed and treated patients per age groups in 2008 and 2009 is shown in Figure 5.3 and Figure 5.4 respectively. This distribution showed that the higher number of diagnosed and treated cases was focused in 2008, around the age group 71-75; in 2009 it was on the age group 66-70. However no direct comparisons can be made as the number of responding centres was dissimilar for 2008 and 2009. Stratification of the treated cases per TNM classification for the responding centres is

presented in Table 5.2 for 2008 and Table 5.3 for 2009 where it can be noted that HIFU is usually performed on T1-T2 patients but not exclusively (some T3 patients have been treated also).

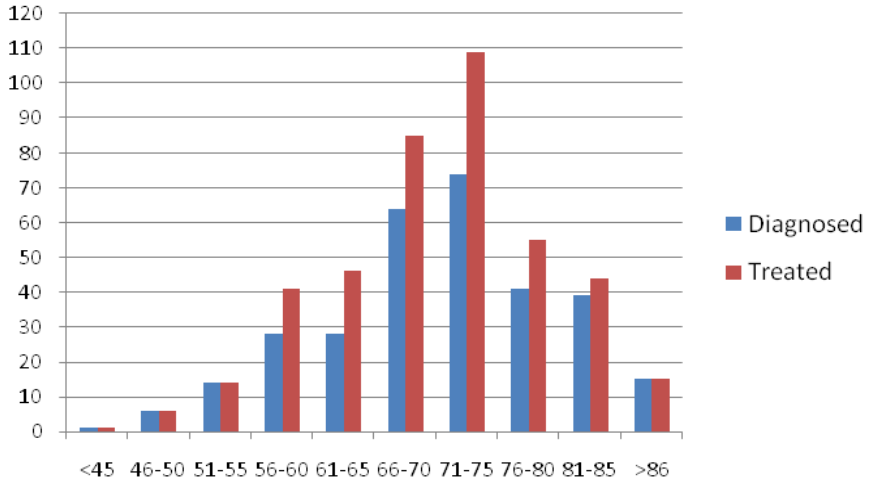
The analysis of the treatment options performed in 2008 and 2009 for prostate cancer is presented in Table 5.4 and Table 5.5. It was not possible to carry out a full analysis of treatments for patients classified as T1 and T2 because data provided from most of the centres were unclear and unreliable. We believe that this may be due to the misunderstanding of the field for the indication of combined treatments (i.e. "Combination (please specify)" at page 2 of the questionnaire in Appendix 4). However Table 5.5 shows that in 3 of the responding centres the population of T1-T2 patients has been split among different treatment options other than HIFU.

Figure 5.2: Number of cases of prostate cancer in 2008 and 2009 (data from 13 of the 14 centres).



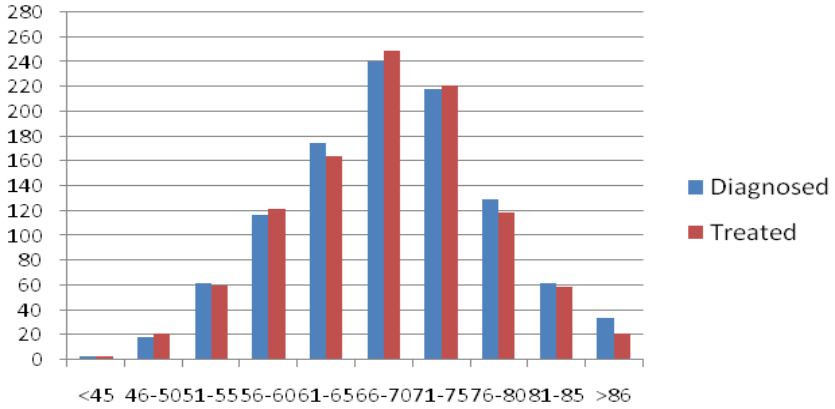
Source: Data from survey analysed by Agenas

Figure 5.3: Stratification of patients by age groups in 2008 (data from 6 of the 14 centres).



Source: Data from survey analysed by Agenas

Figure 5.4: Stratification of patients by age groups in 2009 (data from 13 of the 14 centres).



Source: Data from survey analysed by Agenas

Table 5.2: Stratification of the treated cases in 2008 by TNM classification by responding centres.

Centre	Total treated	TNM				Total treated with HIFU	TNM			
		T1	T2	T3	T4		T1	T2	T3	T4
1	115	45	59	10	1	17	14	2	1	0
2	146	-	-	-	-	19	12	5	2	0
3	-	-	-	-	-	11	3	6	2	0
4	118	60	40	15	3	48	31	12	5	0
5	200	150	120	30	0	73	21	52	0	0
6	-	-	-	-	-	21	0	6	15	0

Source: Data from survey analysed by Agenas

Table 5.3: Stratification of the treated cases in 2009 by TNM classification by responding centres.

Centre	Total treated	TNM				Total treated with HIFU	TNM			
		T1	T2	T3	T4		T1	T2	T3	T4
1	133	20	91	17	5	11	8	3	0	0
2	153	-	-	-	-	9	6	3	0	0
3	136	78	48	11	0	24	10	5	0	0
4	-	-	-	-	-	55	3	6	2	0
5	30	0	25	5	0	9	2	6	1	0
6	113	57	44	9	3	78	-	-	-	-
7	185	67	30	4	0	21	11	8	2	0
8	20	5	2	9	4	13	0	12	1	1
9	131	67	43	17	4	40	25	10	5	0
10	200	150	120	30	0	73	21	52	0	0
11	120	50	40	25	5	13	7	6	0	0
12	350	-	-	-	-	30	5	20	5	0
13	-	-	-	-	-	36	0	16	20	0

Source: Data from survey analysed by Agenas

Table 5.4: Treatments performed for prostate cancer in 2008 (data from one centre).

Treatment options	Number of cases*
Total T1 and T2	**100**
Radical Prostatectomy	58
Radiotherapy	n.r.
Watchful waiting or Active Surveillance	n.a.
Hormonal therapy	n.a.
HIFU	42
Brachytherapy	0
Cryotherapy	0
Laparoscopic Prostatectomy	0
Robotic-Assisted Prostatectomy	0
Combination	0

* data from a single responding centre.

Source: Data from survey analysed by Agenas

Table 5.5: Treatments performed for prostate cancer in 2009 (data from 3 centres).

Treatment options	Number of cases		
	Centre 1	Centre 2	Centre 3
Total T1 and T2	**111**	**101**	**90**
Radical Prostatectomy	69	27	50
Radiotherapy	3	2	5
Watchful waiting or Active Surveillance	10	1	3
Hormonal therapy	18	0	4
HIFU	11	71	13
Brachytherapy	0	0	0
Cryotherapy	0	0	0
Laparoscopic Prostatectomy	0	0	15
Robotic-Assisted Prostatectomy	0	0	0
Combination	0	0	0

Source: Data from survey analysed by Agenas

5.3.3 Case record and details of HIFU treatment (part 3a of 3 of the questionnaire)

The total number of procedures performed with HIFU stratified per centre for both the years 2008 and 2009 are presented in Table 5.6. We reported also the number of HIFU procedures performed as "first-line" treatment and the proportion on the total number of HIFU procedures. This information is useful to show the impact of the use of HIFU on the clinical workload of the centre compared to the other treatment options. For 2008 the treatment rate with HIFU on all the treatment options ranged from 14% to 40% while for 2009 it ranged from 5% to 69% (Table 5.6).

In 2008 HIFU was used as "first-line" treatment in a number of cases that ranged from 36.3% to 81.3%; only one centre used HIFU always as "second-line" treatment. In 2009 HIFU was used as "first-line" treatment with a higher rate, ranging from 57.1% to 100%.

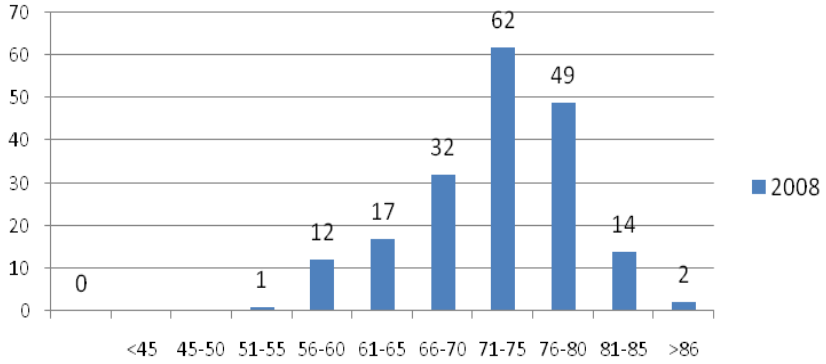
The stratification by age groups of patients treated with HIFU in 2008 and 2009 is presented in Figure 5.5 and Figure 5.6 respectively. Treated patients are mainly in the age groups 71-75 and 76-80.

Table 5.6: Number of HIFU procedures performed in 2008 and 2009.

Centres	2008					2009				
	Total HIFU	HIFU first-line	HIFU not first-line	Total HIFU on HIFU first-line [%]	Patients undergone to TURP before HIFU	Total HIFU	HIFU first-line	HIFU not first-line	Total HIFU on HIFU first-line [%]	Patients undergone to TURP before HIFU
1	17	13	4	76.5	16	11	9	2	81.8	9
2	19	9	10	47.4	14	9	6	3	66.7	1
3	11	4	7	36.4	10	55	40	15	72.7	47
4	-	-	-	-	-	9	9	0	100	9
5	-	-	-	-	-	24	15	7	62.5	15
6	-	-	-	-	-	78	71	7	91.0	66
7	-	-	-	-	-	21	12	9	57.1	10
8	-	-	-	-	-	13	11	2	84.6	10
9	48	39	1	81.3	9	40	25	8	62.5	5
10	73	56	17	76.7	16	73	56	17	76.7	16
11	-	-	-	-	-	13	13	0	100	0
12	-	-	-	-	-	30	27	3	90.0	20
13	21	0	21	0	12	36	-	21	-	36
TOTAL	**189**					**412**				

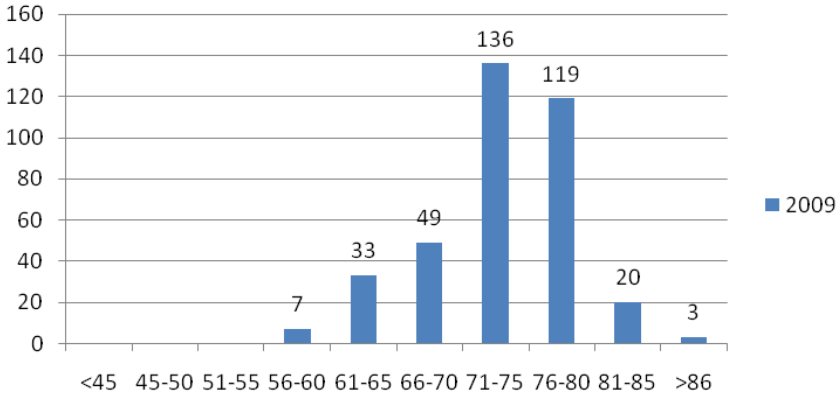
Source: Data from survey analysed by Agenas

Figure 5.5: Number of patients treated with HIFU in 2008 stratified per age groups (6/12 centres).



Source: Data from survey analysed by Agenas

Figure 5.6: Number of patients treated with HIFU in 2009 stratified per age groups (13/14 centres).



Source: Data from survey analysed by Agenas

5.4 Final considerations on the Italian context

The Italian scenario showed a different approach to the collaboration and contribution on the national survey. There was a discernible trend by the type of centres/providers and regions. This aspect played an important role in the result and in the possibility of defining and generalising our conclusions to the whole country. In particular we had a very low response rate from the southern areas although some centres use the HIFU technology.

In addition, even if T1-T2 patients represent the main target population for the treatment, we noted that also T3 patients have been treated with HIFU and a fraction of T1-T2 patients received a different treatment option. A similar consideration can be made about the use of HIFU as "first-line" treatment: it has been used mainly as "first-line" but a part of patients (about 23% in 2009) received the treatment as non first-line (e.g. "second-line").

6. Economic evaluation

6.1 Introduction on economic evaluations

In the assessment of a health technology, the aim of the economic elements together with the other elements is to provide information with a view to improving the basis for decisions in the health care sector through choices between different health technologies, both new and existing. More specifically, the general role of the economic analysis in health technology assessments is to provide information on necessary resource consumption through the use of health technologies and undertake a comparison with the health gains achieved thereby – to assess value for money through the use of a given health technology in preference to another[45].

We intended to perform a cost-effectiveness analysis (CEA) to compare both the costs and consequences arising from use of the HIFU treatment versus the other treatment options. CEA provides a basis for arriving at a conclusion as to which of the technologies/treatments compared is most cost-effective in achieving a given aim and on what scale[45]. Unfortunately, the systematic review of published studies showed a lack of comparative data on effectiveness not allowing us to perform any CEA. We decided to carry out a cost analysis, processing all the costs related to the HIFU treatment as well as those related to the other treatment options.

6.2 Methods

To calculate and compare the costs of all the treatments, we decided to use two sources of information: a literature review of economic studies and the national survey.

According to the latest guidelines[4], HIFU can be thought as an alternative to the following treatment options (see also Chapter 1):

- Watchful Waiting and Active Surveillance (WW and AS);
- Radical Prostatectomy (RP);
- Radiotherapy: EBRT and Transperineal brachytherapy (TB);
- Hormonal Therapy (ADT).

All options are therapeutic treatments (active treatments) for primary prostate cancer with the exception of WW and AS that are non-therapeutic treatments (observational treatments).

We intended to carry out a comparative cost analysis (HIFU versus all the treatment options) by matching data from published studies to those from our context analysis (national survey).

6.2.1 Literature search

We carried out an economic literature review of economic studies published between 2008 and 2010 identified in the main databases: CRD, HEED, PubMed, EMBASE and Cochrane Library. We used that time range as we intended to update searches performed by Obyn et al.[14]. The search strategy for economic studies is described in Appendix 7. We managed our literature findings using ProCite, Version 5 (Windows

2000/98/95NT and Power Macintosh). Citations were analysed in double (MRP and MCo) by reading title and abstract; eligible studies were read in full text and included by applying the inclusion criteria. Disagreements were solved by a third author (TJ).

Inclusion criteria

We decided to differentiate our analysis according to the different types of treatment (i.e. active or observational).

Inclusion criteria for active treatments (RP, EBRT, TB, and ADT) were: all types of economic studies, from 2008 to 2010, reporting resource cost data of RP, EBRT, TB, and ADT for patients with localised prostate cancer, in particular cost data for human resources, drugs, and materials.

Inclusion criteria for observational treatments (WW and AS) were: all types of economic studies, from 2008 to 2010, that reported resource cost data of WW and AS for patients with localised prostate cancer, in particular for visits (medical examinations), biopsies and laboratory exams.

6.2.2 Context analysis

To gather cost and organizational data, we carried out a survey creating a specific economic part in our structured questionnaire; we sent the questionnaire, by e-mail, to the Italian centres that provide the HIFU treatment, asking for data for the years 2008 and 2009. Economic data were collected by part 3 of the survey questionnaire.

- ***Part 3 of 3***

  This part was divided in four specific sub-sections: *a) Case records and details about the HIFU treatment; b) Equipment; c) Human resources used for the HIFU procedure; d) Other resources used for the HIFU procedure*. The analysis of data from sub-section a) has been presented in Chapter 5. In this Chapter we presented the analysis of data from sub-sections b), c), and d).

  a) Case record and details about the HIFU treatment: Information focused on HIFU patients such as type of hospitalization, first-line treatment, number of HIFU sessions, stratification per age groups and TNM, number of patients who underwent TURP (trans-urethral resection of prostate) before the HIFU treatment, intra-procedural complications;

  b) Equipment: Technical as well as economic information on the HIFU system used, its related costs, professional training needed;

  c) Human resources used for the HIFU procedure: Information on the professionals involved in the procedure in terms of type and time;

  d) Other resources used for the HIFU procedure: Information on the setting of the procedure and the disposables and drugs used, in terms of volumes and costs.

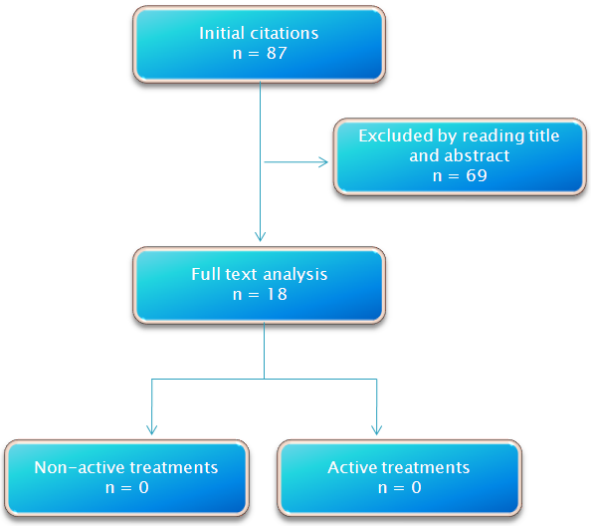
Data were analysed considering the minimum and maximum value for each cost element for the HIFU procedure. The cost elements were: cost of the technology (purchasing and rental), cost of the human resources involved, and cost of drugs/materials/disposables used.

6.3 Results

6.3.1 Evidence from literature

Our searches allowed us to identify 87 studies. After reading titles and abstracts 69 were excluded for inappropriate endpoint (the list of excluded studies is available by the corresponding author). Inclusion criteria were applied to the 18 eligible studies. No studies were included.

Figure 6.1: Flow chart of the economic studies.



6.3.2 Context analysis

In our survey we contacted all the centres (n = 29) that provide the HIFU treatment; we received 14 questionnaires filled out. Because the low response rate we decided to ask to the manufacturer's subsidiary in Italy of the Ablatherm (the most used HIFU system) to integrate the missing data. We received data on type of contract (purchasing or rental) and its costs as well as the costs for maintenance/assistance.

Part 3b - Equipment (Table 6.3 and Table 6.4)

Within the 29 centres, the HIFU system was purchased by 9 centres (one centre bought a second-hand system); 17 centres rented the HIFU technology; 3 centres did not provide this kind of information.

The HIFU system was purchased in the years 2000-2002 by 3 of the 9 centres, 2 centres purchased it in 2003-2004 and 4 centres in 2007-2009.

Among the 17 centres that rented the HIFU system, 6 centres started to provide treatments in the years 2004-2006, 8 centres in 2008-2011, and 3 centres did not provide this kind of information.

The costs linked to the technology were reported by the responding centres in different ways: in terms of cost of purchasing or cost for procedure or cost per year. In particular, all the 9 centres that purchased the HIFU system provided the purchasing cost; among the centres that rented the HIFU system, 3

centres reported the cost per year while 14 centres provided the cost per procedure. The 3 centres that did not provide information on type of contract did not provide information about costs.

To estimate the total cost per procedure for a single HIFU treatment we needed to consider the three following elements: cost of the technology, cost of the human resources involved, and cost of drugs/materials/disposables used.

To estimate the cost of the technology we decided to consider in our analysis only the rental of the technology and not the purchasing as the depreciation time of technology was unknown as well as the average life cycle of the technology; moreover, in many cases, the missing data of the number of procedures performed (not received questionnaires or unclear data) did not allow us to calculate a reliable purchasing cost for procedure.

By the survey we found that the costs for maintenance/assistance were generally included within the type of contract. Only 3 centres reported the annual costs for maintenance/assistance (it ranged from € 57,600 to € 59,136); one centre stated that, inside a contract of "periodic assistance", the annual cost of maintenance depends on the number of patients treated; one centre stated that, inside a contract of "rental", the annual cost of maintenance was € 128,520.

Table 6.3: Purchasing cost of the HIFU systems.

Centre	HIFU system	Starting year	Cost [€]		
			Purchasing	Per procedure	Per year
1	**Ablatherm**	2000	691,000	n.r.	n.r.
2	**Ablatherm**	2001	793,000	n.r.	n.r.
3	**Ablatherm**	2002	725,000	n.r.	n.r.
4	**Ablatherm**	2003	778,000	n.r.	n.r.
5	**Sonablate 500**	2004	350,000	n.r.	n.r.
6	**Ablatherm**	2007	540,000*	n.r.	n.r.
7	**Ablatherm**	2007	624,000	n.r.	n.r.
8	**Ablatherm**	2009	745,000	n.r.	n.r.
9	**Ablatherm**	2009	744,000	3,000	n.r.

** System purchased as second-hand.*

Key: n.r. = not reported.

Source: Data from survey analysed by Agenas

Table 6.4: Rental cost of the HIFU system for the years 2008 and 2009.

Centre	HIFU system	Starting year	Cost [€]	
			Per procedure	Per year
1	**Ablatherm**	2004	2,840	n.r.
2	**Ablatherm**	2005	3,575	n.r.
3	**Ablatherm**	2005	n.r.	6,500 (day)
4	**Ablatherm**	2006	3,120	n.r.
5	**Ablatherm**	2006	3,120	n.r.
6	**Ablatherm**	2006	3,350	n.r.
7	**Ablatherm**	2008	n.r.	(5 y) 190,000+ VAT
8	**Ablatherm**	2008	n.r.	(5 y) 144,045 + VAT
9	**Ablatherm**	2008	3,250	62,000 + VAT
10	**Ablatherm**	2008	3,600	n.r.
11	**Ablatherm**	2009	3,079	n.r.
12	**Ablatherm**	2010	3,200	n.r.
13	**Ablatherm**	2010	3,600	n.r.
14	**Ablatherm**	2008	2,996	n.r.
15	**Ablatherm**	n.a.	3,130	n.r.
16	**Ablatherm**	n.a.	2,800	n.r.
17	**Ablatherm**	n.a.	3,240	n.r.
Average			**3,358**	
Minimum			**2,800**	
Maximum			**3,600**	

Source: Data from survey analysed by Agenas

Key: n.r. = not reported.

Part 3c - Human resources used in the HIFU procedure

We used survey data from 13 centres to calculate costs for the human resources involved in the HIFU procedure (Table 6.5). For a single HIFU procedure the staff involved was: 1 or 2 physicians, 1 or 2 nurses, 0 or 1 assistant, and 0 or 1 other. To link the cost per time spent of all the human resources involved, we considered the National Physician Agreement[46]; according to this Agreement, the cost per unit for a physician is € 43,310.90 gross per year, the cost per unit for a nurse is € 22,093.88 gross per year[47]. We did not consider the cost of "Assistant" and "Other" because it was not possible to identify the gross cost per year because, in case of "Assistant", the resource is strongly linked to the University in which he/she works while for the "Other" category is composed from different types of personnel not clearly identifiable. The working time for physician and nurse is 38 hours per week and 36 hours per week respectively. Time per procedure spent by all the resources involved (average and median) are reported in Table 6.5. We used the Median because it resulted more adherent to data distribution. The cost of the human resources involved calculated per single HIFU procedure is reported in Table 6.6.

Table 6.5: Human resources involved in the HIFU procedure and time spent.

Centre	HIFU System	Human resources involved per procedure				Time spent				
		Physician	Assistant	Nurse	Other	Urologist	Anesthetist	Assistant	Nurse	Other
1	Ablatherm	2	0	2	1	120′	150′	0	150′	15′
2	Ablatherm	2	0	2	1	135′	165′	0	60′	15′
3	Ablatherm	2	1	1	0	120′	120′	120′	120′	0
4	Ablatherm	2	0	1	1	75′	75′	0	75′	30′
5	Ablatherm	3	0	1	1	120′	120′	0	120′	25′
6	Ablatherm	2	0	2	0	150′	150′	0	150′	0
7	Ablatherm	2	0	2	1	180′	180′	0	30′	180′
8	Ablatherm	2	1	1	1	120′	150′	120′	150′	n.a.
9	Sonablate 500	2	0	1	0	120′	165′	0	20′	0
10	Ablatherm	2	0	2	0	120′	120′	0	30′	0
11	Sonablate 500	2	1	1	0	165′	200′	180′	200′	0
12	Ablatherm	2	1	1	1	105′	105′	105′	105′	15′
13	Ablatherm	2	1	1	0	100′	10′	100′	20′	0
Average						**125.38**	**131.54**	**48.08**	**94.62**	**21.54**
Median						**120**	**150**	**0**	**105**	**0**

Source: Data from survey analysed by Agenas

Table 6.6: Cost of the human resources involved in the HIFU procedure.

	Time spent per procedure [minutes]	Cost per year [€ gross]	Working time per week [hours]	Working time per year [minutes]	Cost per minute [€]	Cost per procedure [€]
Physician	120	43,310.90	38	118,560	0.37	43.84
Anesthetist	150	43,310.90	38	118,560	0.37	54.80
Nurse	105	22,093.88	36	112,320	0.20	20.65

Source: Data from survey analysed by Agenas

Part 3d - Other resources used for the HIFU procedure

In all the cases the procedure was performed in an operating theatre, with the exception of one centre that performed it in the endoscopy room.

To estimate the cost of the drugs used, we analysed survey data by category of drugs used, volumes, and prices during and after the HIFU procedure; we consulted our experts to confirm our findings and to identify price ranges.

Drugs identified were:

- during the procedure: "Antibiotics", "Heparin", and " "Gastroprotectors";

- after the procedure: "Painkillers and Anti-inflammatory", "Antibiotics", "Gastroprotectors", and "Heparin".

As drug prices are influenced by several variables (e.g. the contract of purchase, quantity bought and time of payment) we decided to use the list price of the drugs. Price ranges for each drug category are reported in Table 6.7.

Table 6.7: Drugs used during and after the HIFU procedure.

Drugs during procedure		
	Minimum price [€]	**Maximum price [€]**
Antibiotics	2.30	41.50
Heparin	4.48	4.48
Gastroprotectors	8.58	8.58
Drugs after procedure		
	Minimum price [€]	**Maximum price [€]**
Painkillers/anti-inflammatory	0.54	1.23

The cost element "Materials" comes from the sum of "specific kit for HIFU", "kit for anaesthesia" and "other procedure-related disposables" (Table 6.8):

- Specific kit for HIFU: for Ablatherm, the costs ranged from € 662.40 to € 720.00 (data from 2 centres); from other centres resulted that the materials are included in the contract. In the case of Sonablate 500 it was not possible to identify a specific HIFU kit.
- Kit for anaesthesia: for Ablatherm the costs ranged from € 1.50 to € 16.00; for Sonablate 500 such costs were not reported;
- Other procedure-related disposables: for Ablatherm the costs ranged from € 0.98 to €10.00; for Sonablate 500 from € 5.40 to € 16.00.

For the cost element designated as "general disposables" used in the operating theatre the more common disposables were "bladder catheter" (price range € 0.34 - € 13.00), "gloves" (price range € 0.23 - € 2.00) and "saline" (price range € 0.39 - € 10.00) (Table 6.8).

Table 6.8: Drugs, materials and general disposables used for the HIFU procedure.

HIFU system	**Drugs [€]**		**Materials [€]**		**General disposables [€]**	
	Min	**Max**	**Min**	**Max**	**Min**	**Max**
Ablatherm	15.90	55.79	2.48	746.00	0.93	25.00
Sonablate 500	15.90	55.79	5.40	17.00	0.93	25.00

Source: Data from survey analysed by Agenas

6.3.3 Estimate total cost for the HIFU procedure

We estimated the cost per procedure by summing all the cost elements calculated before: cost of the technology, cost of the human resources involved and cost of drugs/materials/disposables used.

We estimated a minimum and maximum total cost per procedure considering the minimum and maximum cost for the Ablatherm HIFU system; it was not possible to estimate the total cost for the Sonablate 500 HIFU system because the main cost elements were not available.

Table 6.9: Cost per procedure estimated using the Ablatherm HIFU system (minimum).

Cost of the HIFU technology (rental fee) [€]	Cost for maintenance/assistance [€]	Cost of the human resources involved [€]	Cost of drugs/materials/disposables [€]	Total
2,800.00	n.e.	119.29	19.31	2,938.60

Source: Data from survey analysed by Agenas

Key: n.e. = not estimable.

Table 6.10: Cost per procedure estimated using the Ablatherm HIFU system (maximum).

Cost of the HIFU technology (rental fee) [€]	Cost for maintenance/assistance [€]	Cost of the human resources involved [€]	Cost of drugs/materials/disposables [€]	Total
3,600.00	n.d.	183.78	826.79	4,610.57

Source: Data from survey analysed by Agenas

Key: n.e. = not estimable.

Due to lack of results from the literature search for economic studies it was not possible to match the data. For the comparison between the cost estimated and the DRG fees, we consulted the TUC 2009 (*Tariffa Unica Convenzionale*, Reimbursement fee from the Italian Ministry of Health)[48] and we linked the HIFU procedure to the DRGs 306 and 307, respectively "Prostatectomy with complications" and "Prostatectomy without complications". This choice was motivated by consultation with our experts. We considered the cost of hospitalisation as the survey showed that all the centres performed the HIFU procedure with this type of admission. The TUC value for both the DRGs is reported in Table 6.11.

Table 6.11: Reimbursement fees linked to "Prostatectomy" (TUC 2009)[48].

DRG	Fee for Hospitalisation [€]
306 (Prostatectomy with complications)	4,630.93
307 (Prostatectomy without complications)	2,868.85

As our survey showed that in some cases the HIFU treatment is performed after the TURP procedure, we included the cost of TURP in the calculation of potential costs of the HIFU procedure.
In particular the procedure is associated to DRGs 336 and 337 (Transurethral Prostatectomy with and without complications respectively). In the Table 6.12 we reported the Fee for Hospitalisation for both the DRGs. In Chapter 5 we reported the number of TURP procedures performed for 2008 and 2009; Table 6.13 shows the percentages of patients who had TURP before HIFU for 2009, because we considered the fee for hospitalisation for 2009.

Table 6.12: Reimbursement fees linked to "Transurethral Prostatectomy" (TUC 2009)[48].

DRG	Fee for Hospitalisation [€]
336 (Transurethral Prostatectomy with complications)	3,574.32
337 (Transurethral Prostatectomy without complications)	2,717.82

Table 6.13: Percentage value of patients who had TURP before HIFU (2009).

Total HIFU procedures	Patients undergone to TURP before HIFU	% TURP before HIFU
412	244	59.22

We linked the estimated "minimum total cost" for HIFU procedure to the DRG for Prostatectomy without complications (DRG 307) and the estimated "maximum total cost" for HIFU procedure to the DRG for Prostatectomy with complications (DRG 306). As in 59.22% of the cases we surveyed it appeared that the TURP has been performed before the HIFU procedure, we summed the fee of the TURP without complications (DRG 337) to the fee of the DRGs 307, and the fee of the TURP with complications (DRG 336) to the fee of the DRG 306, assuming the procedures are provided in two different admissions. In this way we were able to estimate the "minimum total cost" and the "maximum total cost" for the HIFU procedure taking in account also the TURP (Table 6.14 and Table 6.15).

Table 6.14 Estimated minimum total cost of the HIFU procedure compared to the reimbursement fees of DRG 307 and 337 (in 2009 Euros).

HIFU procedure cost (Minimum)	Fee of Prostatectomy	Fee of TURP	Total
	DRG 307	DRG 337	DRG 307 + DRG 337
2,938.60	2,891.80	2,717.82	5,609.62

Table 6.15 Estimated maximum total cost of the HIFU procedure compared to the reimbursement fees of DRG 306 and 336 (in 2009 Euros).

HIFU procedure cost (Maximum)	Fee of Prostatectomy	Fee of TURP	Total
	DRG 306	DRG 336	DRG 306 + DRG 336
4,610.57	4,667.98	3,574.32	8,242.30

Another variable to consider in the calculation of the estimate cost of the HIFU procedure is the post-interventional pathway. The HIFU procedure is a non-invasive treatment aimed at curbing the progress of the disease; on the other hand, Prostatectomy is a surgical intervention that works directly on the organ affected (by resecting it). This difference between the two treatment options generates a different approach in the post-intervention phase, for example requiring more monitoring of the HIFU patients (e.g. periodic medical examinations, byopsies, etc.) compared to those who undergo Prostatectomy. These monitoring may generate additional costs that we did not consider in our evaluation. In addition, we have not taken into account the costs associated with complications of treatment including fistulas, rectal injury, urinary and sexual symptoms, many of which may require ongoing and or costly interventions in addition to the impact on patient quality of life.

6.4 Discussion

HIFU technology if widely used in Italy; Ablatherm is by far the most common and used HIFU system (used by all the centres with the exception of two that use Sonablate 500). Rental, which is offered only from the manufacturer's subsidiary of Ablaterm, is the most common type of acquisition of the technology (only 9 of the 29 centres purchased the HIFU system).

For a HIFU session, the typical staff is composed by: urologist, anaesthetist and one or two nurses; the procedure is performed within an operating theatre.

To our knowledge this is the first attempt at estimating the costs related to the HIFU procedure (no studies were identified by our searches). Our cost analysis showed that the estimated total cost of the HIFU procedure, assuming specific hypotheses (e.g. linking the reimbursement of the HIFU procedure to specific DRGs and considering only the rental of the HIFU system), has a similar value to the DRG fee linkable to such procedure (i.e. Prostatectomy), even though the DRG refers to a surgical intervention. It is very important to highlight that in about 60% of the surveyed cases, a TURP was needed as preliminary to HIFU and this increases the final total cost.

7. Considerations on patient's acceptability

7.1 Introduction

After the diagnosis of prostate cancer, a plethora of treatment options is usually presented to the patient. All these treatments are associated with adverse effects ranging from physical (e.g. incontinence, bleeding, gastrointestinal toxicity, erectile dysfunction) to psychological (the "emotional burden" of the disease)[49] and all have impact on quality of life (QoL).

In the case of localised prostate cancer implementing strategies to assist the patient in the choice is a complex issue. Many patients with low risk disease may be enrolled on active surveillance delaying or perhaps avoiding definitive treatment and the related side effects.

The patient's sense of identity, particularly his masculine identity and sexuality, as well as the overall well-being is affected by any treatment. It's hard to justify severe adverse effects in the cases in which the disease is likely not to be lethal (e.g. in low risk cancer, in men of advanced age or significant co-morbid status). Guidelines for the diagnosis and treatment of prostate cancer recommend that healthcare professionals should discuss all treatment options including adverse effects of each treatment. Studies reported that some patients may prefer maintaining their potency and quality of life rather than potentially securing longer term survival through treatment with radiotherapy or surgery[50]. Patient information is crucial, as well as the surgeon's knowledge of the latest evidence on the topic. At present, little evidence is available to support a survival advantage for any particular treatment that could help make patient choice clearer[51].

7.2 Treatment versus observational cancer management strategies

Prostate cancer may have slow progression and, considering its prevalence in men with a relatively short life expectancy (around a half of the cases occur in men over 70 years) and considering that some patients can live several years without curative treatments, active surveillance (or watchful waiting) is proposed as an option. No adverse events can be associated to active surveillance but this strategy has a negative effect on QOL: for example, the study by Arredondo et al. on 310 men diagnosed with prostate cancer reported decreases in the physical domain scores as well as sexual function scores in the group under watchful waiting. The START trial *(NCT00499174: Study of active surveillance Therapy Against Radical Treatment in patients diagnosed with Favourable-risk prostate cancer)*[52] which started in 2007 will give some indication in this field as it aims to compare the disease-specific survival of patients who have favourable-risk disease treated with radical prostatectomy or radiotherapy at the initial diagnosis with that of patients whose treatment is active surveillance and selective intervention. The study will use a number of QoL instruments to observe the impact of treatments on QoL[49] (see Table 7.1[53–56]).

Thus the potential adverse events and long-term complications associated with each option are critical considerations in selecting cancer management strategy.

There is no definitive evidence for the superiority of any one treatment over the others and the advantages and risks of each are still debated. The best treatment is related to the patient's age, his health status, the cancer stage, the personal preference, and surgeon's skillset[2].

In our opinion, more serious discussion has to take place on the widespread use of prostate-specific antigen (PSA) screening. According to the review by Djulbegovic et al.[57] the existing evidence from RCT does not support the routine use of screening for prostate cancer with PSA with or without digital rectal examination. Ironically, earlier diagnosis and treatment of prostate cancer can adversely affect patient well-being more than the disease itself.

As there is still debate on the optimal treatment of an individual patient we suggest careful consideration of the effect of each approach on QoL as well as cancer-related outcome.

Data to guide the choice should be available in the next few years as several trials[57] are ongoing and expected to provide further evidence of the benefits and harms of screening as well as the effect of subsequent treatment choices in patients with positive results.

- **ProtecT study**: based in the UK, the "Prostate testing for cancer and Treatment" trial[58] and its extension, the ProtecT-CAP (Comparison Arm for trial ProtecT)[59] are ongoing and will report their final results around 2013 and 2015, respectively. About 1,500 were randomised to radical surgery, conformal radiotherapy, or active surveillance.
- **PIVOT trial**: based in the US, from 1994 to 2002, the "Prostate cancer Intervention Versus Observation Trial" randomised 731 men from an ethnically diverse background to either radical prostatectomy or active surveillance[60]. Final results should be published within the next two years.
- **START trial:** based in Canada the "Surveillance Therapy Against Radical Treatment" trial is planning to randomise 2,130 men with low risk localised prostate cancer to active surveillance versus early interventions with curative intent[61].

Expected within the next years are also results from the complete follow-up and full reporting of the PLCO trial[62], ERSPC[63], French ERSPC[64], and Gothenburg trial[65].

Table 7.1: Adverse effects associated with standard treatments (adapted from Singh et al. 2010[66]).

Treatment	Benefits	Limitations
Active surveillance/watchful waiting	• Avoids treatment of insignificant cancer • Not risks of side effects from surgery or radiation	• Potential "anxiety" from not treating a diagnosed cancer • Regular rectal exams, PSA testing with periodic/multiple biopsy to monitor • Possibility that "window of curability" may be missed
Radical prostatectomy	• Accurate pathologic staging • Allows PSA to be more reliable marker of disease control • Trials demonstrate reduction in prostate cancer specific deaths • Allows potential for nerve sparing procedure • Long term outcome data available (for open radical prostatectomy) • Compared to radiation treatments, less issues with urinary frequency or urgency, rectal and bowel irritation • Salvage possible with EBRT	• Surgical risks (infection, bleeding, reaction to anesthesia, etc) • For laparoscopic/robotic technique: additional risk of intrabdominal injury or pneumoperitoneum related complications; limited long term outcome data at present • Limited physical activity in recovery period (2–4 weeks) • Post op complications of incontinence: 5%–20% (usually stress); erectile dysfunction: up to 50% at 5 years (with nerve preservation, may be improved by medical therapy); bladder neck contractures 1%–3%; lymphocele with retropubic approach; rare rectal injury
External beam radiation therapy (EBRT) (normofractionation)	• Avoids hospital stay and risk of surgery • Outpatient, limited impact on daily living • Long term cancer control reported • Addition of hormonal therapy improved cancer control for high risk • Incontinence rare (1%–2%) • Urinary retention less common than with brachytherapy	• No post-treatment staging information • Daily treatments for 6–8 weeks • Fatigue may occur when treatment ends • Erectile dysfunction: up to 50% at 5 years • Bowel/rectal problems: 5%–10% (urgency, pain, diarrhea, or bleeding) but typically improve after treatment • Bladder irritation: 5% (urinary frequency, urgency, discomfort) • Salvage therapies limited or associated with high complication rate
Stereotactic body radiotherapy (hypofractionation)	• "Convenient" outpatient treatments as short as five days	• Utility and side effect profile not well studied
Brachytherapy	• Minimal surgical risks, one time outpatient surgical procedure • Best for low risk prostate cancer • Delivers higher dose to prostate target, less to surrounding tissues • Long term data available • Low rate of incontinence (1%–2%)	• Not useful for intermediate or high risk cancer • Very small and very large glands (<20 cc, >80 cc) challenging • No final pathologic staging • Less favorable option for men with intermediate- or high-risk disease • Not recommended for men with significant lower urinary tract symptoms • Urinary tract side effects (retention, urgency, frequency) more common than with other therapies • ED outcomes similar to EBRT • Salvage therapies limited or associated with high complication rate
Proton beam therapy	• Ability to deliver dose to prostate and avoid other structures	• Most costly infrastructure of all treatments • No trials to demonstrate superiority over current radiation modalities • Limited number of facilities
Cryotherapy	• One time treatment, often outpatient • Can be repeated • Allows for potential "focal" therapy	• No final pathology • Side effect profiles can be difficult to manage, but improving with newer techniques • High rate of ED for whole gland therapy

8. Discussion

The aims of the present HTA report were to:

i) Assess and analyse effectiveness and safety data from the scientific literature on HIFU treatment of localised prostate cancer compared to other treatment options;

ii) Describe the level of adoption and utilisation of the HIFU technology in Italian clinical practice;

iii) Perform an economic analysis on the utilisation of the technology in Italy;

iv) Assess patient acceptability.

As we made clear in Chapter 4, evidence from our systematic review did not allow us to make a final statement about the comparative effectiveness of HIFU ablation versus the other options. No RCTs or other comparative studies had been published at the time of our searches. None are available at the time of writing (20 July 2011). All the 23 included studies were non-comparative and we believe that the lack of trials is the main problem in the field of medical devices and surgical interventions assessment[44].

However so far only non-comparative retrospective studies have been published reporting on large groups of patients[67] for long follow-up periods[68].

As the HIFU treatment purportedly confers advantages in domains related to quality of life and patient-related outcomes, associated to its minimally invasive nature, all future studies should take into account these domains and highlight them in a clearer fashion.

According to the latest EAU Guidelines[4] HIFU is not considered as an alternative treatment for the localised treatment of prostate cancer but as an "experimental" treatment. However we suggest considering HIFU as an investigational treatment since the mechanisms of action and short term effectiveness are already known but long-term data are expected.

As comparative effectiveness could not be extracted from published studies, we were not able to perform any cost-effectiveness analysis. We described our cost analysis with an estimate of the estimate total cost per procedure for the HIFU treatment. In the survey we found that around 60% of HIFU patients received concomitant TURP; this is similar to what observed in the studies included (65% of patients).

Our analysis tried to identify the real use of the HIFU in our country and, despite some limits due to relatively slow returns of questionnaire, we tried to carry out a transparent analysis, integrating the missing relevant data (for example, purchasing cost of technology and rental cost) with information from other sources (the manufacturer's subsidiary in Italy). Moreover, our total costs did not include the androgen deprivation therapy that in 10 of the 23 studies has been administrated after the HIFU treatment in 20% to 66% of the treated patients. We recognise that our analysis under-estimates costs but it can provide a general cost overview.

It is essential to inform the patient properly. Some patients prefer maintaining their sexual function and quality of life rather than have a longer term survival after a curative approach[50]. At the time of writing,

little evidence is available to support a survival advantage for any particular treatment that could help make patient choice clearer[51]. The ongoing trials should show soon if observational management of prostate cancer is a good solution for prostate cancer.

In February 2011 the French National Authority for Health (HAS - Haute Autorité de Santé) granted Ablatherm HIFU treatment temporary reimbursement authorization under a special regimen for innovative therapies (source: www.edap-tms.com). This is happening more than 10 years after obtaining CE marking. In Italy a specific reimbursement fee for HIFU does not exist; however, given its diffusion in the whole country, this does not function as a disincentive.

9. Recommendations

We recommend:

- Performing HIFU ablation of localised prostate cancer in T1-T2 patients as an investigational treatment until comparative effectiveness will be generated (e.g. comparative studies, registers).
- When evidence will be available and support the use of the HIFU technology, it is important to define strategies to gather all the related costs to plan proper HIFU-specific reimbursement fees.

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Agenas takes sole responsibility for the final form and content of this report. The views expressed in this report do not necessarily represent the views of the Italian Ministry of Health or any regional government.

11. Competing interests declaration

The Authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

List of acronyms and abbreviations

ADT	androgen deprivation therapy.
AGREE	appraisal of guidelines research & evaluation instrument (www.agreecollaboration.org).
AS	active surveillance.
BPH	benign prostatic hyperplasia.
CE mark	certification and testing of products for the European market.
CEA	cost-effectiveness analysis.
CRD	centre for reviews and dissemination of the University of York (www.york.ac.uk/inst/crd).
DRE	digital rectal examination.
DRG	diagnosis-related group.
EAU	European association of urology (www.uroweb.org).
EBRT	external beam radiation therapy.
FDA	United States food and drug administration (www.fda.gov).
HEED	health economic evaluations database.
HIFU	high intensity focused ultrasound.
HTA	health technology assessment.
IPSS	international prostate symptom score.
IPSS-QoL	international prostate symptom score-quality of life index.
LDR	low dose radiation.
NHS	national health service.
NHT	neoadjuvant hormonal therapy.
PSA	prostate-specific antigen.
Q-max	assessment of the maximum urinary flow rate.
QoL	quality of life.
RCT	randomised controlled trials.
RDM	medical device repertory (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).
RP	radical prostatectomy.
SDO	hospital discharge record.
TB	transperineal brachitherapy.
TNM	system for classifying the extent of cancer spread.
TUC	*Tariffa unica convenzionale*.

TURP	trans-urethral resection of the prostate.
UCLA-PCI	UCLA prostate cancer index.
WW	watchful waiting.

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Appendix 1

Table A.1: Description of treatment options for primary prostate cancer (T1-T2)[4].

Treatment	Description
Watchful waiting	Also known as "deferred treatment" or "symptom-guided treatment". Is a conservative management of prostate cancer until the development of local or systemic progression, at which point the patient would be treated palliatively with TURP or other procedures for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions.
Active Surveillance	Also known as "active monitoring". Is a conservative management of prostate cancer and includes an active decision not to treat the patient immediately and to follow him with close surveillance and treat at pre-defined thresholds that classify progression (i.e. short PSA doubling time and deteriorating histopathological factors on repeat biopsy). In these cases, the treatment options are intended to be curative.
Radical prostatectomy (RP)	RP involves the removal of the entire prostate gland between the urethra and the bladder, and resection of both seminal vesicles along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by a bilateral pelvic lymph node dissection. In men with localised prostate cancer and a life expectancy > 10 years, the goal of an RP by any approach must be eradication of disease, while preserving continence and whenever possible potency. There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone. Rather, increasing co-morbidity greatly increases the risk of dying from causes not related to prostate cancer. An estimation of life expectancy is paramount in counselling a patient about surgery.
Radiotherapy: - EBRT - Transperineal brachytherapy	*EBRT (external beam radiation therapy)* 3D-CRT is the most used EBRT; anatomical data, acquired by scanning the patient in a treatment position, are transferred to the 3D treatment planning system, which visualises the clinical target volume and then adds a (surrounding) safety margin. At the time of irradiation, a multi-leaf collimator automatically adapts to the contours of the target volume seen by each beam. Real-time verification of the irradiation field allows for comparison of the treated and simulated fields, and correction of deviations where displacements occur. Whatever the techniques and their sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists.
	Transperineal brachytherapy: Also known as "interstitial radiation therapy" or "seed implantation". It can be with low- (LDR) or high-dose (HDR) rate and consists in the implantation of radioactive seeds (titanium-encased pellets containing a radioisotope) within the prostate permanently or not. The patient is positioned in a dorsal decubitus gynaecological position. Implantation is undertaken by endorectal sonography and under general anaesthesia or spinal block, and involves a learning curve for the whole team: the surgeon for delineation of the prostate and needle placement, the physicist for real-time dosimetry, and the radiation oncologist for source loading. The sonography probe introduced into the rectum is fixed in a stable position.
Hormonal therapy (ADT)	Testosterone, although not carcinogenic, is essential for the growth and perpetuation of prostate cells (thus also of tumour cells). If prostate cells are deprived of testosterone stimulation, they undergo apoptosis. Any treatment that results ultimately in suppression of androgen activity is referred to as ADT (androgen deprivation therapy). ADT can be achieved by: i) suppressing the secretion of testicular androgens by surgical or medical castration; ii) inhibiting the action of the circulating androgens at the level of their receptor in prostate cells using competing compounds known as anti-androgens; iii) combinations of these two methods, commonly known as CAB.

Key: TURP = transurethral resection of the prostate; EBRT = external beam radiation therapy; 3D-CRT = three-dimensional conformal radiotherapy; CAB = complete androgen blockade.

Appendix 2

Search strategy for secondary literature review

Sources (by the Cochrane Library)

- Cochrane database of Systematic Review
- Database of abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database

Keywords

Searches of the databases were carried out on 6th October 2010, using the following keywords and mix of keywords to specify:

- **the technology of interest:** *HIFU, High intensity focused ultrasound, Robotic HIFU, Ablatherm, Sonablate.*
- **the indication of interest***: Prostate cancer, PCa, prostatic carcinoma, localized prostate cancer, localized PCa, low risk prostate cancer, intermediate risk prostate cancer, prostatic neoplasm, prostatic neoplasia, prostate tumor, prostate adenocarcinoma.*

Time limit

Study published from 2000 to the time of searches (6th October 2010).

Search strategy

#1 HIFU OR "High focused ultrasound" OR "Robotic HIFU"

#2 Ablatherm

#3 Sonablate

#4 (#1 OR #2 OR #3) [TECNOLOGIA]

#5 prostate AND (cancer OR tumor OR adenocarcinoma)

#6 "prostate cancer" AND (localized OR "low risk" OR "intermediate risk")

#7 prostatic AND (carcinoma OR neoplasm OR neoplasia)

#8 PCa Or "localized PCa"

#9 (#5 OR #6 OR #7 OR #8)

#10 (#4 AND #9)

Search results and list of excluded studies for secondary literature review

Search results

Number of citations found = 11

Number of citation considered for full text analysis = 5 (see Chapter 4 and Bibliography)

Number of citation excluded = 6

Reason for exclusion: language

Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT). High intensity focused ultrasound (HIFU) for the treatment of localised prostate cancer (Ablatherm(R) system) (Project record). HTA-32005000807. Paris: Comite D'Evaluation Et De Diffusion Des Innovations Technologiques (CEDIT). 2005.

Reason for exclusion: study design/type of document

Chaussy, C. and Thüroff, S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. CN-00437582. Current Urology Reports. 2003; 4(3):248-52.

National Institute for Clinical Excellence. High-intensity focused ultrasound for prostate cancer (Structured abstract). HTA-32005000191. London: National Institute for Clinical Excellence (NICE). 2005; 2.

National Institute for Clinical Excellence. High-intensity focused ultrasound for prostate cancer (Information from Interventional Procedure Guidance 118). London: National Institute for Clinical Excellence (NICE). 2005. ISBN: 1-84257-906-1.

Reason for exclusion: topic

Lam Thomas BL, Simpson Mary, Pennet Linda, Nabi Ghulam, Gillatt David, Swami S, N'Dow James MO, British Association of Urological Surgeons (BAUS), Section of Oncology, McClinton Samuel, Shelley Mike. Surgical Management of Localised Prostate Cancer. Cochrane Database of Systematic Reviews: Protocols 2008 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007021. 2008; (2).

Li, L. Y.; Yang, M.; Gao, X.; Zhang, H. B.; Li, J. F.; Xu, W. F.; Lin, Z., and Zhou, X. L. Prospective comparison of five mediators of the systemic response after high-intensity focused ultrasound and targeted cryoablation for localized prostate cancer. CN-00719022. BJU International. 2009; 104(8):1063-7.

Appendix 3

Search strategy for primary literature review

Sources

- Medline
- Embase
- The Cochrane Library

Keywords

Searches of the databases were carried out on 17th December 2010, using the following keywords and mix of keywords to specify:

- **the technology of interest:** *HIFU, High intensity focused ultrasound, Robotic HIFU, Ablatherm, Sonablate.*
- **the indication of interest***: Prostate cancer, PCa, prostatic carcinoma, localized prostate cancer, localized PCa, low risk prostate cancer, intermediate risk prostate cancer, prostatic neoplasm, prostatic neoplasia, prostate tumor, prostate adenocarcinoma.*

Restrictions on the publication time

Studies published from 1st January 2000 to the time of searches (6th October 2010).

Restriction on language

Studies published in English or in Italian

Medline:

Restrictions on the population type and on the study design

Studies on humans;

Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Clinical Conference, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Research Support, American Recovery and Reinvestment Act, Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S, Technical Report, English, Italian.

Search strategy

#1 "prostate cancer" OR "prostate cancers"

#2 "prostatic neoplasms" [mesh]

#3 "prostate tumor" OR "prostate tumors"

#4 "prostate adenocarcinoma"

#5 "prostatic carcinoma"

#6 "prostatic neoplasia"

#7 PCa

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 (localized AND #8)

#10 ("low risk" AND #8)

#11 ("intermediate risk" AND #8)

#12 (#9 OR #10 OR #11) [POPOLAZIONE]

#13 HIFU

#14 "High-intensity focused ultrasound"

#15 "Robotic HIFU"

#16 Ablatherm

#17 Sonablate

#18 (#13 OR #14 OR #15 OR #16 OR #17) [INTERVENTO]

#19 (#12 AND #18)

Embase:

Restrictions on the population type

Studies on humans;

Search strategy

#23. #15 AND #22

#22. #16 OR #17 OR #18 OR #19 OR #20 OR #21

#21. sonablate

#20. ablatherm

#19. 'robotic hifu'

#18. 'high-intensity focused ultrasound'/exp

#17. high AND intensity AND focused AND 'ultrasound'/exp

#16. 'hifu'/exp

#15. #10 OR #12 OR #14

#14. #8 AND #13

#13. 'intermediate risk'

#12. #8 AND #11

#11. 'low risk'

#10. #8 AND #9

#9. localized

#8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#7. pca

#6. 'prostatic neoplasia'/exp

#5. 'prostatic carcinoma'/exp

#4. 'prostate adenocarcinoma'/exp

#3. 'prostate tumor'/exp OR 'prostate tumors'

#2. 'prostate tumor'/exp

#1. 'prostate cancer'/exp OR 'prostate cancers'

The Cochrane Library:

Search strategy

#1	MeSH descriptor Prostatic Neoplasms explode all trees
#2	(prostate cancer):ti,ab,kw or (prostate cancers):ti,ab,kw
#3	(prostate tumor):ti,ab,kw or (prostate tumors):ti,ab,kw
#4	(prostate adenocarcinoma):ti,ab,kw
#5	(prostatic carcinoma):ti,ab,kw
#6	(prostatic neoplasia):ti,ab,kw
#7	(PCa):ti,ab,kw
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	(localized)
#10	(#8 AND #9)
#11	(low risk)
#12	(#8 AND #11)
#13	(intermediate risk)
#14	(#8 AND #13)
#15	(#10 OR #12 OR #14)
#16	(High intensity focused ultrasound)
#17	(HIFU)
#18	(Robotic HIFU)
#19	(Ablatherm)
#20	(Sonablate)
#21	(#16 OR #17 OR #18 OR #19 OR #20)
#22	(#15 AND #21)
#23	(#22), from 2000 to 2010

List of excluded studies from the primary literature review

Number of citation excluded = 18

Reason for exclusion: population

Ficarra, V., et al., Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU International, 2006. 98(6): p. 1193-8.
(High risk patients)

Reason for exclusion: topic

Uchida, T., et al., The effect of neoadjuvant androgen suppression on prostate cancer-related outcomes after high-intensity focused ultrasound therapy. BJU International, 2006. 98(4): p. 770-2.
(Effect of pharmacological therapy)

Uchida, T., et al., To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? BJU International, 2006. 98(3): p. 537-9.
(Predictors of treatment failure)

Blana, A., et al., Factors predicting for formation of bladder outlet obstruction after high-intensity focused ultrasound in treatment of localized prostate cancer. Urology, 2008. 71(5): p. 863-7.
(Predictors of treatment failure)

Ganzer, R., et al., PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. European Urology, 2008. 53(3): p. 547-53.
(Predictors of treatment failure)

Sumitomo, M., et al., Efficacy of short-term androgen deprivation with high-intensity focused ultrasound in the treatment of prostate cancer in Japan. Urology, 2008. 72(6): p. 1335-40.
(Effect of pharmacological therapy)

Biermann K. Montironi R. Lopez-Beltran A. Zhang S. Cheng L. Histopathological findings after treatment of prostate cancer using high-intensity focused ultrasound (HIFU). Prostate (2010) 70:11 (1196-1200).
(Histopathological characterization)

Sumitomo M. Asakuma J. Yoshii H. Sato A. Horiguchi A. Ito K. Nagakura K. Asano T. Anterior perirectal fat issue thickness is a strong predictor of recurrence after high-intensity focused ultrasound for prostate cancer. International Journal of Urology (2010) 17:9 (776-782)
(Predictors of treatment failure)

Reason for exclusion: outcomes

Li L.-Y. Yang M. Gao X. Zhang H.-B. Li J.-F. Xu W.-F. Lin Z. Zhou X.-L. Prospective comparison of five mediators of the systemic response after high-intensity focused ultrasound and targeted cryoablation for localized prostate cancer. BJU International (2009) 104:8 (1063-1067)
(Comparative but not relevant outcomes)

Li L.-Y. Lin Z. Yang M. Gao X. Xia T. Ding T. Comparison of Penile Size and Erectile Function after High-intensity Focused Ultrasound and Targeted Cryoablation for Localized Prostate Cancer: A Prospective Pilot Study. Journal of Sexual Medicine (2010) 7:9 (3135-3142)
(Comparative but not relevant outcomes)

Shoji S. Nakano M. Nagata Y. Usui Y. Terachi T. Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: A prospective study. International Journal of Urology (2010) 17:8 (715-719).
(Not relevant outcomes)

Reason for exclusion: design of the study

Blana, A., et al., Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology, 2008. 72(6): p. 1329-33; discussion 1333-4.
(Retrospective)

Misrai, V., et al., Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. World Journal of Urology, 2008. 26(5): p. 481-5.
(Retrospective)

Barua J. Campbell I I. Cole O. Harris D. Kaisary A. Larner T. Miller P. Nigam R. Mumtaz F. Thilagarajah R. Thompson A. Brown S. High-intensity focused ultrasound for localized prostate cancer: Initial experience with a 2-year follow-up. BJU International (2009) 104:11 (1794)
(Letter)

Dudderidge T. Ahmed H. Emberton M. High-intensity focused ultrasound for localized prostate cancer: Initial experience with a 2-year follow-up. BJU International (2009) 104:8 (1170-1171)
(Letter)

Crouzet S. Rebillard X. Chevallier D. Rischmann P. Pasticier G. Garcia G. Rouviere O. Chapelon J.-Y. Gelet A. Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. European Urology (2010) 58:4 (559-566)
(Retrospective)

Ripert T. Azemar M.-D. Menard J. Bayoud Y. Messaoudi R. Duval F. Staerman F. Transrectal high-intensity focused ultrasound (HIFU) treatment of localized prostate cancer: Review of technical incidents and morbidity after 5 years of use. Prostate Cancer and Prostatic Diseases (2010) 13:2 (132-137).
(Retrospective)

Reason for exclusion: duplication
Obyn C. Mambourg F. Assessment of high intensity focused ultrasound for the treatment of prostate cancer. Acta Chirurgica Belgica (2009) 109:5 (581-586).
(Published within a citation already assessed)

Appendix 4

Questionnaire

Introduction

This document is aimed to collecting data on the procedure for the treatment of prostate cancer ablation using HIFU (High Intensity Focused Ultrasound). In particular we intend to investigate the effectiveness and safety of the HIFU treatment for localized prostate cancer in a specific group of patients, such as men with localized prostate cancer (T1-T2), at low or intermediate risk, receiving first-line treatment with curative intent.
This investigation is carried out by the National agency for regional healthcare (Agenas) on the behalf of the Ministry of Health, within the national Health Technology Assessment (HTA) program.
This questionnaire has been sent to all the centres that provide the HIFU procedure for the National Health Service (NHS). The data collected will be used for the production of an assessment report (HTA report) that will be published and disseminated by the Ministry of Health web portal (www.salute.gov.it) and the Agenas website (www.agenas.it).

Please fill out the whole questionnaire using exclusively this electronic format inserting "X" or editing the data (text or numeric) within the boxes.
For any additional information or problems, please refer to the accompanying letter or contact directly the Agenas offices (**MR Perrini, 0642-749344; A Migliore, 0642-749447**).

Part 1 of 3
HEALTHCARE PROVIDER AND CONTACTS

Reference year		2009
		2008
Healthcare provider type		General Hospital
		Specialised Hospital / Medical School
		Private Clinic
		Research Hospital
		Health Centre
		Other (please specify):
Name of the healthcare provider		
Department		
Address		
Head of Department	Surname and name	
	Phone	e-mail:
Contact for the survey	Surname and name	
	Phone	e-mail:

Part 2 of 3
POPULATION AND CLINICAL PATHWAYS

Number of cases of prostate cancer diagnosed in the year	**N.=**		
Number of cases of prostate cancer treated in the year	**N.=**		
Distribution of diagnosed patients by age groups	**Age**	**Number of patients**	
	<45		
	46-50		
	51-55		
	56-60		
	61-65		
	66-70		
	71-75		
	76-80		
	81-85		
	>86		
Distribution of treated patients by age groups	**Age**	**Number of patients**	
	<45		
	46-50		
	51-55		
	56-60		
	61-65		
	66-70		
	71-75		
	76-80		
	81-85		
	>86		
Distribution of treated cases by TNM classification	**TNM**	**Number of patients**	
	T1		
	T2		
	T3		
	T4		
Distribution of treated cases by prognostic group	**Group**	**Number of patients**	
	I		
	IIa		
	IIb		
	III		
	IV		
Number of T1 and T2 patients treated with radical prostatectomy	**N.=**		
Number of T1 and T2 patients treated with radiotherapy	**N.=**		

Number of T1 and T2 patients received other pathways/treatments:

Watchful waiting or Active Surveillance	**N.=**	Cryotherapy	**N.=**
Hormonal therapy	**N.=**	Laparoscopic Prostatectomy	**N.=**
HIFU	**N.=**	Robotic-Assisted Prostatectomy	**N.=**
Brachytherapy	**N.=**	Combination (please specify):	**N.=**

Key: N. = number.

Part 3 of 3
a) CASE RECORDS AND DETAILS ABOUT TREATMENT

Total number of HIFU procedures performed in the year for prostate cancer	**N.=**	
Number of patients treated by type of hospitalization		**Number of patients**
	Inpatient	
	Day-hospital/Day-surgery	
	Outpatient	
Number of patients treated with HIFU as first-line treatment with curative intent	**N.=**	
Number of patients treated with HIFU not as first-line	**N.=**	
In how many sessions the HIFU procedure has been performed?	1 session N. = 2 sessions N. = 3 sessions or more N. =	
Distribution of patients treated with HIFU by age groups	**Age**	**Number of patients**
	<45	
	46-50	
	51-55	
	56-60	
	61-65	
	66-70	
	71-75	
	76-80	
	81-85	
	>86	
Distribution of patients treated with HIFU by TNM classification	**TNM**	**Number of patients**
	T1	
	T2	
	T3	
	T4	
Distribution of patients treated with HIFU by prognostic group	**Group**	**Number of patients**
	I	
	IIa	
	IIb	
	III	
	IV	
Number of patients who underwent TURP (trans-urethral resection of prostate) before the HIFU treatment	**N.=**	
Number of medical examinations during the following 12 months after the procedure	**N.=**	
Number of cases with intra-procedural complications	**N.=**	
	- Urethro-rectal fistula N.= **- Other (please specify):**	
Please specify how the complications were resolved	*(please insert text here)*	

Key: N. = number.

Part 3 of 3
b) EQUIPMENT

HIFU system		**Ablatherm**	
		Sonablate 500	
	Year of acquisition		
	Purchase price *(EUR VAT included)*		
	Renting fee per procedure *(EUR VAT included)*		
Further elements *(specify only if purchased separately; e.g. dedicated pc, dedicated printer)*	**Element description**		**Cost** *(EUR VAT included)*
Maintenance/Assistance	**Contract type** (e.g. periodically, on call)		**Cost/year** *(EUR VAT included)*
Specific training	**Who was trained**		**- Physicians N. =** **- Assistants N. =** **- Nurses N. =**
	Training time *(please specify hours or days)*		
	Training costs (total)		

Key: N. = number.

Part 3 of 3
c) HUMAN RESOURCES USED FOR THE HIFU PROCEDURE

Physician	**Speciality**	
	Time (in minutes)	
Assistants	**Number of units**	
	Time (in minutes)	
Anaesthetist	**Time (in minutes)**	
Nurses	**Type**	
	Number of units	
	Time (in minutes)	
Other professionals	**Type**	
	Number of units	
	Time (in minutes)	

70

Part 3 of 3
d) OTHER RESOURCES USED FOR THE HIFU PROCEDURE

HIFU procedure setting	☐	**Operating room**	
	☐	**Other (please specify)**	
	Procedure time (minutes)		
	Mean number of stay (days)		
Drugs *(please specify type and dosage)*	**Intra-operative** *(e.g. antibiotics)*		
	Post-operative *(e.g. analgesics)*		
Procedure-related disposables	**Description**	**Cost** *(EUR VAT included)*	
	Specific HIFU kit		
	Anaesthesia kit		
	Other (please specify):		
Disposables used in the intra-operative	**Description**	**Number of units**	**Cost per unit** *(EUR VAT included)*
Disposables used in the pre- and post-operative phase	**Description**	**Number of units**	**Cost per unit** *(EUR VAT included)*

Appendix 5

Centres involved in the survey

Centre	Regions
Azienda Ospedaliera "A. Cardarelli"	Campania
ASL Caserta 1 PO Piedimonte Matese	Campania
AUSL SA/1 PO Umberto I di Nocera Inferiore	Campania
Ospedale Pierantoni di Forlì	Emilia-Romagna
Presidio Ospedaliero di Carpi - Azienda USL di Modena	Emilia-Romagna
Azienda Ospedaliera - Università di Parma	Emilia-Romagna
Azienda Ospedaliera Santa Maria Degli Angeli	Friuli Venezia Giulia
Azienda per i servizi sanitari n.2 Isontina - Ospedale di Gorizia	Friuli Venezia Giulia
Università Cattolica del Sacro Cuore	Lazio
Villa Tiberia s.r.l.	Lazio
Casa di Cura INI	Lazio
Azienda Ospedaliera Universitaria Policlinico Tor Vergata	Lazio
Ospedale S. Anna di Como	Lombardia
Casa di Cura Santa Maria/PO di Castellanza	Lombardia
Spedali Civili di Brescia	Lombardia
Casa di Cura Villa Serena	Marche
Azienda Ospedaliera S. Giovanni Battista	Piemonte
Casa di Cura Santa Rita	Piemonte
Ospedale San Giovanni Bosco	Piemonte
Azienda Ospedaliera "Di Venere Giovanni XXIII"	Puglia
Istituto San Raffaele - G.Giglio di Cefalù	Sicilia
Health in future urology s.r.l. c/o Casa di Cura Candela	Sicilia
AOU Policlinico G. Martino di Messina	Sicilia
Ospedali SS Giacomo e Cristoforo Massa	Toscana
Casa di Cura Rugani	Toscana
Universita' degli Studi di Perugia - Clinica Urologica - Osp. S.Andrea delle Fratte	Umbria
Casa di Cura Abano Terme	Veneto
Azienda Ospedaliera di Padova	Veneto
PO di Este - Azienda ULSS 17	Veneto

Appendix 6

Responding centres

Centre	Regions	Head of department	Contact for the survey
Ospedale Pierantoni di Forlì	Emilia-Romagna	Dr. T Zenico	Dr. C Salaris
Azienda Ospedaliera - Università di Parma	Emilia-Romagna	Prof. P Cortellini	Dr. UV Maestroni
Azienda Ospedaliera Santa Maria degli Angeli	Friuli Venezia Giulia	Dr. A Garbeglio	Dr. D Maruzzi
Università Cattolica del Sacro Cuore	Lazio	Prof. PF Bassi	Dr. F Pinto
Villa Tiberia s.r.l.	Lazio	Dr. R Giulianelli	Dr. F Pisanti
Casa di Cura INI Grottaferrata	Lazio	Dr. F De Marco	Dr. L Grillenzoni
Casa di Cura Santa Maria/PO di Castellanza	Lombardia	Dr. G Comeri	Dr. G Comeri
Spedali Civili di Brescia	Lombardia	Prof. S Cosciani Cunico	Dr. C Rosati Dr. P Piovanelli
Casa di Cura Villa Serena Jesi	Marche	Dr. M Magagnini	Dr. M Magagnini
Ospedale San Giovanni Bosco	Piemonte	Prof. G Muto	Dr. L D'Urso
Ospedali SS Giacomo e Cristoforo Massa	Toscana	Dr. V Vocaturo	Dr. V Vocaturo
Universita' degli Studi di Perugia - Clinica Urologica - Osp. S.Andrea delle Fratte	Umbria	Prof. M Porena	Dr. L Mearini
Azienda Ospedaliera di Padova	Veneto	Prof. F Zattoni	Prof. V Ficarra
PO di Este - Azienda ULSS 17	Veneto	Dr. A Calabrò	Dr. L Pizzol

Appendix 7

Search strategy for economic studies

Sources

- Embase
- Medline
- NHS EED (Economic Evaluation Database NHS) of the Centre for Review and Dissemination (CRD)

Keywords

Searches of the databases were carried out on 19th May 2011, using the following keywords and mix of keywords to specify:

- **Population:** *prostate cancer, PCa, prostatic carcinoma, localized prostate cancer, localized PCa, low risk prostate cancer, intermediate risk prostate cancer, prostatic neoplasm, prostatic neoplasia, prostate tumor, prostate adenocarcinoma.*
- **Economic analysis***: Cost analysis, cost effectiveness, CEA, cost utility, CUA, health care costs, economic evaluation, economic analysis, economic aspect, economic assessment, economic comparison, QALY.*
- **Intervention:** *HIFU, High intensity focused ultrasound, Robotic HIFU, Ablatherm, Sonablate.*
- **Comparator:** *Radiotherapy, radiation therapy, external beam radiation therapy; EBRT, Radical prostatectomy, prostatectomy; Hormonal therapy, androgen deprivation, antiandrogen therapy; Active surveillance; "active monitoring", Watchful waiting, "deferred treatment", "symptom guided treatment".*

Time limit

Study published from 2008 to the time of searches (19th May 2011).

Restrictions on language

Studies on humans published in English or in Italian.

Embase:

Restrictions on the population type and on the study design

Studies on humans;

Search strategy

#1 "prostate cancer" OR "prostate cancers"

#2 "prostatic neoplasms"

#3 "prostate tumor" OR "prostate tumors"

#4 "prostate adenocarcinoma"

#5 "prostatic carcinoma" OR "prostatic neoplasia"

#6 PCa

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

#8 (localized AND #7)

#9 ("low risk" AND #7)

#10 ("intermediate risk" AND #7)

#11 (#8 OR #9 OR #10)

#12 HIFU OR "High-intensity focused ultrasound" OR "Robotic HIFU"

#13 Ablatherm OR Sonablate

#14 (#12 OR #13)

#15 "Cost analysis" OR "health care costs"

#16 "cost effectiveness" OR CEA

#17 "cost utility" OR CUA

#18 "economic evaluation" OR "economic analysis" OR "economic aspect" OR "economic assessment" OR "economic comparison"

#19 QALY

#20 (#15 OR #16 OR #17 OR #18 OR #19)

#21 Radiotherapy OR "radiation therapy" OR "external beam radiation therapy" OR EBRT

#22 "Radical prostatectomy" OR prostatectomy

#23 "Hormonal therapy" OR "androgen deprivation" OR "antiandrogen therapy"

#24 "Active surveillance" OR "active monitoring"

#25 "Watchful waiting" OR "deferred treatment" OR "symptom guided treatment"

#26 (#21 OR #22 OR #23 OR #24 OR #25)

#27 (#11 AND #14 AND #20)

#28 (#11 AND #20 AND #26)

#29 #27 AND limit ing/it Humans 2008-2011

#30 #28 AND limit ing/it Humans 2008-2011

Medline:

Restrictions on the population type and on the study design

Studies on humans;

Search strategy

#1 "prostate cancer" OR "prostate cancers"

#2 "prostatic neoplasms" [mesh]

#3 "prostate tumor" OR "prostate tumors"

#4 "prostate adenocarcinoma"

#5 "prostatic carcinoma"

#6 "prostatic neoplasia"

#7 PCa

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 (localized AND #8)

#10 ("low risk" AND #8)

#11 ("intermediate risk" AND #8)

#12 (#9 OR #10 OR #11)

#13 HIFU

#14 "High-intensity focused ultrasound" [mesh]

#15 "Robotic HIFU"

#16 Ablatherm

#17 Sonablate

#18 (#13 OR #14 OR #15 OR #16 OR #17)

#19 "Cost analysis" OR "health care costs"

#20 "cost effectiveness" OR CEA

#21 "cost utility" OR CUA

#22 "economic evaluation" OR "economic analysis" OR "economic aspect" OR "economic assessment" OR "economic comparison"

#23 QALY

#24 (#19 OR #20 OR #21 OR #22 OR #23)

#25 Radiotherapy OR "radiation therapy" OR "external beam radiation therapy" OR EBRT

#26 "Radical prostatectomy" OR prostatectomy

#27 "Hormonal therapy" OR "androgen deprivation" OR "antiandrogen therapy"

#28 "Active surveillance" OR "active monitoring"

#29 "Watchful waiting" OR "deferred treatment" OR "symptom guided treatment"

#30 (#25 OR #26 OR #27 OR #28 OR #29)

#31 (#12 AND #18 AND #24)

#32 (#12 AND #24 AND #30)

#33 (#31 OR #32)

#34 (#33 Limits: Humans, English, Italian, Publication Date from 2008/06/01 to 2011)

The Cochrane Library (NHS EED):

Restrictions on the population type and on the study design

Studies on humans;

Search strategy

#1	MeSH descriptor Prostatic Neoplasms explode all trees
#2	(prostate cancer):ti,ab,kw or (prostate cancers):ti,ab,kw
#3	(prostate tumor):ti,ab,kw or (prostate tumors):ti,ab,kw
#4	(prostate adenocarcinoma):ti,ab,kw
#5	(prostatic carcinoma):ti,ab,kw OR (prostatic neoplasia):ti,ab,kw OR (PCa):ti,ab,kw
#6	(#1 OR #2 OR #3 OR #4 OR #5)
#7	(localized AND #6)
#8	(low risk AND #6)
#9	(intermediate risk AND #6)
#10	(#7 OR #8 OR #9)
#11	(High intensity focused ultrasound)
#12	(HIFU) OR (Robotic HIFU)
#13	(Ablatherm) OR (Sonablate)
#14	(#11 OR #12 OR #13)
#15	“cost analysis” OR “health care costs”
#16	“cost effectiveness” OR CEA
#17	“cost utility” OR CUA
#18	“economic evaluation” OR “economic analysis” OR “economic aspect” OR “economic assessment” OR “economic comparison”
#19	QALY
#20	(#15 OR #16 OR #17 OR #18 OR #19)
#21	Radiotherapy OR “radiation therapy” OR “external beam radiation therapy” OR EBRT
#22	“Radical prostatectomy” OR prostatectomy
#23	“Hormonal therapy” OR “androgen deprivation” OR “antiandrogen therapy”
#24	“Active surveillance” OR “active monitoring”
#25	“Watchful waiting” OR “deferred treatment” OR “symptom guided treatment”
#26	(#21 OR #22 OR #23 OR #24 OR #25)
#27	(#10 AND #14 AND #20)
#28	(#10 AND #20 AND #26)
#29	(#28 AND limit 2008-2011)

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